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TAPEWORM ANEMIA

THERAPEUTIC OBSERVATIONS *

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The cause of the anemia which appears in a small percentage of persons harboring *Dibothryocephalus latus* (*Diphyllobothrium latum*) has not received, as yet, an adequate explanation. Ehrström [1] estimated that in Finland, where from 250,000 to 275,000 inhabitants are *Dibothryocephalus* hosts, only from 0.1 to 0.5 per cent of those infected with the tapeworm develop anemia. A correspondingly small percentage was noted in other countries. Ehrström pointed out that anemia may appear in a small, but relatively almost as frequent a, percentage of patients infected with *Taenia saginata, T. solium* and *Ascaris lumbricoides*. Piney,[2] among others, noting its close resemblance to pernicious anemia, suggested that it may be a form of this type of anemia which has been elicited in susceptible persons by the toxins of the tapeworms. A constitutional predisposition plus the stimulus given by the tapeworm gives rise, in the host, to symptoms and signs which are frequently indistinguishable from those of pernicious anemia in noninfected persons. Schauman [3] noted relapses in some patients many years after the expulsion of the parasites, even in the absence of reinfection. He also noted true pernicious anemia in relatives of patients with anemia who were infested. It has been suggested that the tapeworms may be macerated or otherwise abnormal in those who developed anemia, and that the intact and healthy tapeworm is not harmful to the host in this respect. This observation, however, has not been confirmed in all cases. Schau-

* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

1. Ehrström, Robert: Zur Frage des gastrointestinalen Ursprungs der perniziösen Anämie, Ztschr. f. klin. Med. **105**:106, 1927.

2. Piney, A.: Recent Advances in Haematology, Philadelphia, P. Blakiston's Son & Co., 1927, p. 71.

3. Schauman, O., quoted from Piney (footnote 2, p. 71).

man and Tallqvist [4] and others [5] have found that the proglottids of the tapeworm may contain 10 per cent (of solids) of cholesterol oleate. This substance, while hemolytic in vitro, is apparently not effective on parenteral injection. The ground up bodies of the tapeworms, however, exert a hemolytic action both in the test tube and in the body. The active substance is alcohol soluble and is bound to the tissues but not to the lipoids (Syderhelm [6]). The presence of a hemolytic substance in the tapeworm does not account, however, for the differences in reaction of the hosts.

The resemblance of the blood picture to that of pernicious anemia suggests that a similar mechanism affecting the hemopoietic system may be present in both diseases. As Minot and Murphy [7] had shown that the blood of patients with pernicious anemia could be restored to normal when ½ pound (227 Gm.) of liver was eaten daily, this regimen was tried on a patient having a marked anemia and *Dibothryocephalus latus* infection.

REPORT OF CASE

The patient was a well developed, obese, white woman, aged 53. She was born in Russia (Lithuania), but at the age of 10 years came to America and lived in Detroit. Her father was living and well at the age of 70, but her mother had died of pernicious anemia two years previous to the patient's admission to the hospital. The physician who treated the mother reported that she had had "an undoubted case of pernicious anemia, with typical blood picture, cord symptoms, palpable spleen and occasional petechiae. The stools were negative for blood and ova." [8] Three sisters and three brothers, as well as the husband, did not show signs of anemia. The patient had been married for thirty years and had had ten children. One died at birth following a "dry labor," and one at the age of 7 months of pneumonia. She had not had any miscarriages. After the tenth pregnancy a "laparotomy with sterilization" was performed, resulting in an artificial menopause. The only previous illness of note was an attack of "bronchitis" about three years previous to the present admission. She was then confined to her bed for three weeks.

The chief complaint during the present illness was "weakness." This had started insidiously about two years previously, with loss of appetite and increased nervous irritability. About five months before admission, the fatigue and weakness became more marked and the patient noted some numbness of her fingers. She also noted that her feet were dragging and that she could not walk as well as previously. Apparently there was no change in sensation, except that the lower extremities felt heavy. Later, she had a moderate diarrhea which lasted three

4. Schauman, O., and Tallqvist, T. W.: Ueber die blutkorperchenauflösenden Eigenshaften des breiten Bandwurms, Deutsche med. Wchnschr. **24**:312, 1898.

5. Tallqvist, T. W.: Zur Pathogense der perniziösen Anämie, mit besonderer Berücksichtigung der Bothriozephalusanämie, Ztschr. f. klin. Med. **61**:427, 1907.

6. Syderhelm, R.: Zur Pathogenese der perniziösen Anämien, Deutsches Arch. f. klin. Med. **126**:95, 1918.

7. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926.

8. Mayer, W. D.: Personal communication to the author.

or four days. This disappeared spontaneously, but some epigastric distress with gaseous distention and a tendency to belch remained. During the month preceding this she had noticed a sore tongue. "Blisters" appeared on her lips and tongue, and the latter was reddened. Her gums were frequently swollen, but she attributed this to irritation from her false teeth.

About two years before the present examination, the patient noted two lengths of a flat tapeworm, one about 2 feet (60.9 cm.) long. She never noticed any more after that. The source of the infection is not clear. The patient was always fond of fish, having been in the habit of eating white fish, perch or pike at least twice a week. Little meat or vegetables were eaten. Other members of the family did not show evidence of infestation, and eggs were not found in their stools.

The outstanding features on physical examination were the intense yellowish pallor of the skin and mucous membranes. The hair and the iris of the eyes were dark brown. The fundi did not show evidence of hemorrhages. The tongue was smoother than normal but was not atrophied. A large abdominal hernia was present at the region of a medial scar from the laparotomy. The heart appeared normal. The systolic blood pressure was 135; diastolic, 70. The lungs showed

TABLE 1.—*Differential Leukocyte Count*

	Per Cent		Per Cent
Polymorphonuclear neutrophils, adult	29.5	Myeloblasts	1.5
Polymorphonuclear neutrophils, young	6.0	Small lymphocytes	20.5
Polymorphonuclear eosinophils	1.0	Large lymphocytes	25.5
Polymorphonuclear basophils	0.5	Monocytes	2.0
Myelocytes	1.0	Crushed cells	7.5
Metamyelocytes	4.0	Hemohistioblasts	1.0

TABLE 2.—*Measurements of Red Blood Cells*

	Per Cent		Per Cent
3.75 microns	1.5	9.00 microns	21.5
4.50 microns	3.5	9.75 microns	10.5
5.25 microns	2.5	10.5 microns	2.5
6.00 microns	5.5	11.25 microns	2.0
6.75 microns	9.5	12.0 microns	1.5
7.50 microns	18.5	12.75 microns	0.5
8.25 microns	20.5		

evidence of a mild bronchitis. The spleen was not palpable, but the edge of the liver was soft and palpable 8 cm. below the costal margin. The reflexes were slightly more active than normal, and the vibration sense was within normal limits. Her best weight had been 150 pounds (68 Kg.) seven years previously. She had lost weight during the latter part of the illness, so that when she presented herself at the hospital she weighed 117½ pounds (53.3 Kg.).

The temperature during the first eight days in the hospital ranged from 99 to 102 F., being lower in the morning and higher in the evening and reaching normal on the fifth day after the administration of liver was begun and remaining normal thereafter. Free hydrochloric acid was not found in the fasting gastric contents or in three successive fractions taken at half hour intervals after a gastric test meal. Blood was not found in the gastric contents. The stools showed many eggs of *Dibothryocephalus* (*Diphyllobothrium*) *latus*, but blood was not found. The blood count on admission showed 1,940,000 red blood cells per cubic millimeter, 6,600 white blood cells per cubic millimeter and 33 per cent hemoglobin (Sahli). The differential leukocyte count is shown in table 1.

The measurements of the cells on admission are shown in table 2.

The red blood cells were hyperchromic. There was 1.5 per cent of reticulocytes. Moderate poikilocytosis was present, and many of the large red blood cells were oval. There were 264 nucleated red blood cells per cubic millimeter. Most of the nucleated red blood cells were of macronormoblast type, but numerous megaloblasts were found. Stippled red blood cells and some with Howell-Jolly bodies, Cabot's rings and nuclear particles were present. Some of the large red blood cells were round or irregular, with uniform staining and an absence of a clearcut edge. Some of the microcytes were pale, and some were stippled. The platelets were slightly decreased in number.

In view of Macht's[9] observation on the inhibitory effect of pernicious anemia serum on the growth of lupin seedlings in Shive's solution (prepared by mixing 10.4 cc. of 0.5 molar solution of calcium nitrate, 30 cc. of 0.5 molar solution of magnesium sulphate, and 36 cc. of 0.5 molar monopotassium acid phosphate with distilled water sufficient to make 1 liter) the serum of the patient was tested on

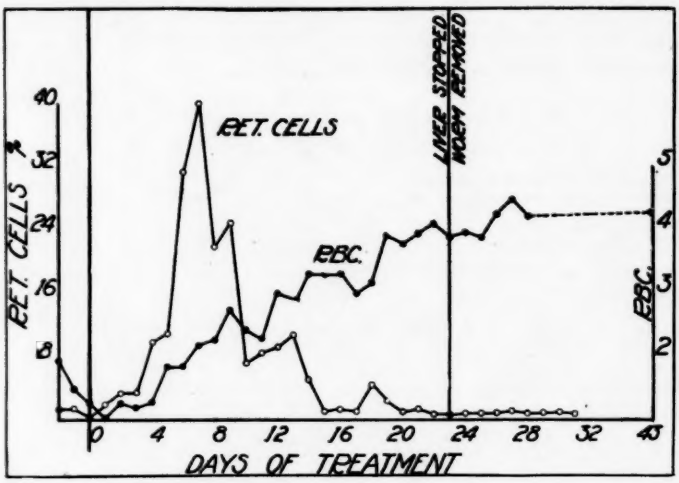

Fig. 1.—Graph showing changes in the red blood cell count and reticulocyte percentage during the course of treatment.

two occasions, one before the tapeworm was removed and when the red blood cell count was 1,220,000 per cubic millimeter, and the other after the removal of the worm and when the red blood cell count was 4,210,000 per cubic millimeter. On the first occasion the growth was 60 per cent of that of the control, and on the second occasion the growth was 75.2 per cent of the growth of the control in twenty-four hours. There was definite inhibition of growth by the serum taken from the patient before the treatment with liver was started, commensurate with that which Macht outlined for the blood of persons with pernicious anemia.

The bile indexes and quantitative bilirubin (van den Bergh) readings are given in table 3.

The patient was treated with ½ pound of raw, finely ground, calf's liver daily, and during this time antihelminthic medication was not given. Her blood responded just as that of a patient with typical pernicious anemia, with a rise in

9. Macht, D. I.: Etiology, Diagnosis and Treatment of Pernicious Anemia, J. A. M. A. **89**:753 (Sept. 3) 1927.

the reticulocyte percentage to 39 per cent, followed by a return to almost normal, and then a second rise to 11.6 per cent. The hemoglobin percentage rose steadily, and there was a definite rise in the red blood cell count. When the blood count was approaching normal (on November 4, fig. 1), the patient received six doses of 1 cc. each of oleoresin of aspidium in capsules while fasting, after a preliminary

TABLE 3.—*Data of Bile Index and Bilirubin Readings*

	Bile Index	Van den Berg (Indirect)
October 14	60	1.5 milligrams per cent
October 18	15	1.2 milligrams per cent
October 28	5	0.9 milligrams per cent
November 2	5	0.4 milligrams per cent

TABLE 4.—*Changes in Blood Counts with Progress of Disease*

Date	Red Blood Cells (Millions per Cu. Mm.)	White Blood Cells (per Cu. Mm.)	Hemoglobin (per Cent)	Reticulated Red Blood Cells (per Cent)	Therapy
Oct. 12	1.94	6,600	33	1.5	
Oct. 13	1.45	3,800	33	1.7	
Oct. 14	....	.....	..	2.2	
Oct. 15	1.31	5,850	28	0.6	Feeding of liver started
Oct. 16	1.10	6,050	30	2.0	
Oct. 17	1.29	4,400	28	3.3	
Oct. 18	1.22	9,550	28	3.5	
Oct. 19	1.32	14,750	28	11.8	
Oct. 20	....	.....	29	13.1	
Oct. 21	1.81	8,700	34	31.4	
Oct. 22	2.15	8,350	40	39.9	
Oct. 23	2.37	6,400	41	20.7	
Oct. 24	2.77	7,750	50	27.0	
Oct. 25	2.43	5,750	50	7.2	
Oct. 26	2.34	8,500	50	8.1	
Oct. 27	3.06	8,050	50	9.0	
Oct. 28	2.87	7,350	55	11.6	
Oct. 29	3.28	8,850	53	5.4	
Oct. 30	3.31	8,850	55	7.3	
Oct. 31	3.30	8,400	54	1.0	
Nov. 1	3.02	10,150	63	1.6	
Nov. 2	3.21	9,500	64	1.5	
Nov. 3	3.90	10,900	64	4.5	
Nov. 4	3.71	10,550	63	2.4	Antihelminthic medication; tapeworms expelled; feeding of liver discontinued
Nov. 5	3.93	10,700	68	1.0	
Nov. 6	4.09	12,250	63	1.1	
Nov. 7	3.65	11,300	62	0.7	
Nov. 8	3.70	15,900	62	0.7	
Nov. 9	3.63	10,800	63	0.8	
Nov. 10	4.16	12,150	64	0.2	
Nov. 11	4.49	11,050	63	1.0	
Nov. 12	4.19	11,550	64	1.1	
Nov. 13	4.30	11,650	66	0.7	
Nov. 14	3.85	13,650	61	0.8	
Nov. 15	4.21	11,250	65		
Nov. 28	4.25	11,750	71	0.8	
Jan. 10	4.96	7,450	70		
March 12	4.41	5,950	60		

treatment with magnesium sulphate. Two tapeworms of the *Dibothryocephalus latus* type were passed, one about 9 feet (274 cm.) long and the other about 12 feet (365.8 cm.) long, when measured under slight tension. One was pinkish gray, the other slightly yellower. Except for a few terminal segments which were macerated, the tapeworm appeared in good condition.

After the expulsion of the tapeworms, the eggs were no longer found in the stools. Ingestion of liver was discontinued, and a regular diet without liver or kidneys was prescribed. Improvement continued without interruption.

In order to determine the presence of toxin in *Dibothryocephalus latus* and the possibility of absorption of this toxin by the patient, 20 Gm. of the tapeworm was ground in a mortar with 200 cc. of physiologic sodium chloride solution until the tapeworm was entirely emulsified. This mixture was then placed in a bottle and shaken for fifteen minutes and filtered through filter paper and then through a Berkefeld filter. The filtrate was cultured aerobically and anaerobically to insure sterility, and when this was confirmed, 0.1 cc. of the sterile filtrate was injected intradermally into the patient and also into a normal person.

The patient did not show at any time a wheal formation at the point of injection. She was therefore not sensitized cutaneously to the toxins or proteins of soluble nature in the tapeworm. At the end of eighteen hours, at the point of

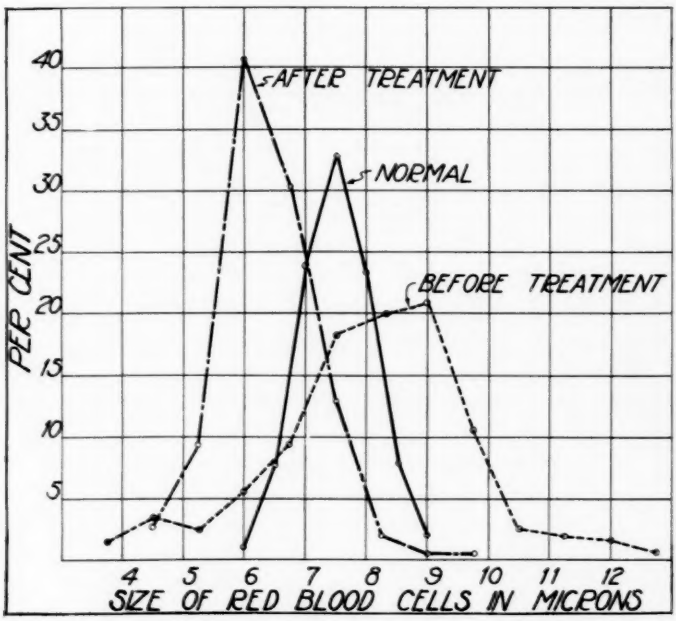

Fig. 2.—Graph showing the measurements of the red blood cells before and after treatment, in comparison with those of normal persons.

injection, both the control and the patient showed a small area of erythema 1 cm. in diameter. This demonstrated that there was little toxic material in the tapeworm substance and that the patient was not immunized to the small amount of toxin present. Presumably, therefore, she had not been absorbing toxic metabolic products from the parasite. The degree of toxin present is in no way comparable to that obtained from streptococci and other common organisms, because soluble filtrates from these organisms in 1:100 dilution produce large areas of erythema. The dilution of the tapeworm filtrate used was 1:10.

Table 4 shows the changes in the blood counts with the progress of the disease.

As the patient improved, the red cells approached normal in size and shape. A comparison of the size of the cells at the beginning of the treatment with those at the end of the treatment is shown in figure 2.

The patient's weight on discharge was 122 pounds (55.3 Kg.). She appeared normal in all respects and was found to be perfectly healthy during five months of subsequent observation during which liver or kidneys were not eaten. She gained in weight and felt well. On March 12, 1928, five months after the patient was first examined, free hydrochloric acid was not found in the stomach contents one-half, one and one and a half hours after a gastric test meal.

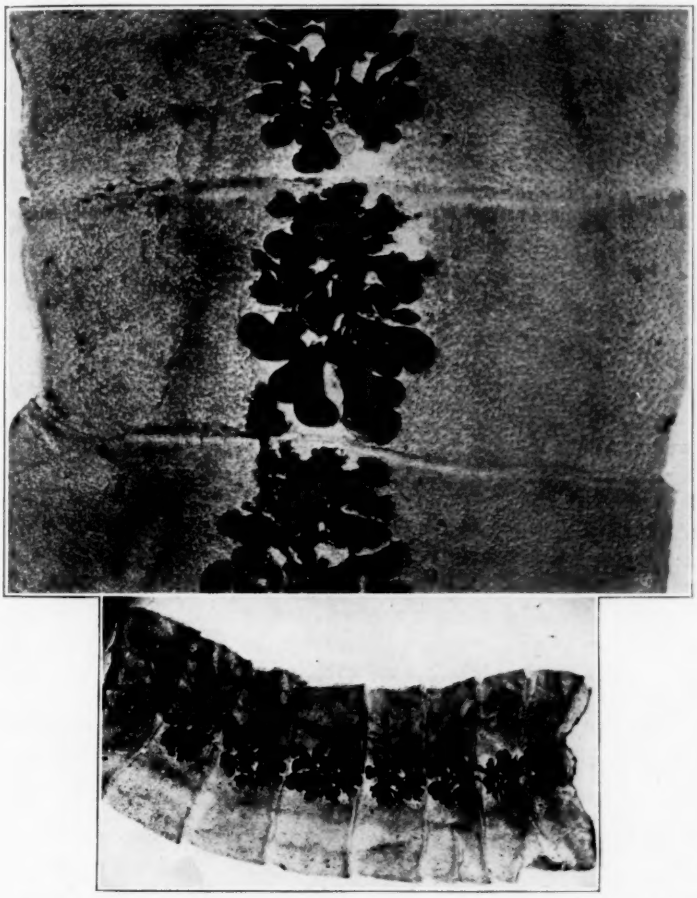

Fig. 3.—Segments of Dibothryocephalus latus (Diphyllobothrium latum) tapeworm injected with india ink to show the configuration of the uterus (Isaacs: J. Lab. & Clin. Med. **7**:691, 1922).

COMMENT

The interesting features of the case are the resemblance to pernicious anemia, as has been noted frequently in the literature, and the improvement in the blood picture on a therapeutic regimen for pernicious anemia.

The infection probably originated in Russia. The anemia usually disappears in this type of infection with the removal of the parasite, but in this case the anemia was decreased even when the parasites were still present. There is evidently some substance in liver which must counteract the anemia producing mechanism both in the addisonian as well as in this type of anemia. In both are found a macrocytic anemia (here 59 per cent of the red blood cells were 8.25 microns or larger), an increase in bilirubin, achlorhydria, fever and gastro-intestinal and neurologic symptoms with features that go with a deficiency in red blood corpuscles. In these respects the two diseases appear identical, lending some support to the concept that *Dibothryocephalus* infection is one of the possible mechanisms by which a pernicious anemia-like condition may be elicited in susceptible persons. The presence of pernicious anemia in the family (the mother) is confirmatory of this.

The relatively high icterus index and bilirubin content of the blood serum before treatment was started indicate that there was increased pigment metabolism, presumably from the hemolysis of red blood corpuscles. A possible hemolytic agent is found in the tapeworm, but there is apparently an additional factor necessary in the host before the material can be absorbed in amounts sufficient to cause marked destruction of red blood cells as so few of the carriers of the tapeworm develop anemia. The disease, however, does not appear to be primarily a hemolytic anemia. The presence of true megaloblasts in the peripheral blood stream and the increase in the number of reticulated red blood cells in the blood after liver feeding indicate that the bone marrow is in a state of hyperplasia with the bulk of the cells in an immature (nucleated) state. The leukopenia, accompanied by the presence of immature white blood cells as well as atypical and pathologic forms, is confirmatory of this, as this is the change that accompanies the malignant hyperplasia of immature erythroblastic tissue, as shown by Peabody and others. After recovery, the general "leukocyte picture" was more normal, although an occasional metamyelocyte was noted, as well as a pathologic lymphocyte. The lymphocyte count and percentage remained high (41.5 per cent on Jan. 10, 1928). Although one may expect an eosinophilia in an infection with tapeworm, the percentage did not increase in this case until after the feeding of liver was started. This may have been a "liver response" such as has been noted after feeding liver to patients with pernicious anemia by Watkins and Berglund [11] and by Whitby [12] and others. While the percentage of

10. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **3**:179, 1927.

11. Watkins, Charles H., and Berglund, Hilding: Analysis of Morphological Blood Changes in Pernicious Anemia Following Administration of Liver, Proc. Soc. Exper. Biol. & Med. **25**:206, 1927.

12. Whitby, L. E. H.: Leucocytic Changes Resulting from the Treatment of Pernicious Anemia with Liver, Lancet **214**:285, 1928.

eosinophils varied from 0 to 2.5 before the treatment with liver was started, it reached 5 per cent seven days later, 6 per cent in the second week and 8 per cent two months after removal of the tapeworm. As liver was not eaten during these two months, the persistent eosinophilia must have been related to some other factor.

The persistent achlorhydria resembles that of addisonian pernicious anemia.

The liver diet was discontinued after the expulsion of the tapeworm in order that the further progress without the special diet could be noted. Improvement continued, as it usually does in such cases. It is possible, of course, that this case may have been one of true pernicious anemia with an incidental infection with tapeworm. Apparently all cases of *Dibothryocephalus* anemia are not as characteristic of the addisonian type as this one.

SUMMARY

A case of *Dibothryocephalus latus* (*Diphyllobothrium latum*) anemia is described in which the blood picture, increase in bilirubin, achlorhydria, fever, neurologic and other clinical symptoms were indistinguishable from those of pernicious anemia. The patient's mother had died of pernecious anemia. It was found possible to cause a hematopoietic remission, with disappearance of the symptoms, by feeding liver daily, even though the parasite was not removed. Removal of the parasite, which was effected later by the administration of oleoresin of aspidium, accompanied the continuance of the convalescence. Evidence for the presence of soluble toxins was not obtainable from intradermal tests with saline suspensions of the tapeworm.

DANGER OF THE ADMINISTRATION OF EPHEDRINE IN HEART FAILURE*

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While ephedrine has been employed in Chinese medicine for over five thousand years, it has been only in the past five years, since its reisolation and careful study by Chen and Schmidt, that modern medicine has added it to the list of drugs in daily use. In 1923, Chen called attention to ephedrine and conducted a careful study of its physiologic effect, so that in a short time the drug became popularized and freely used by practitioners of medicine and even by laymen.

At the present time, the drug is widely used for a variety of conditions, and the literature contains many interesting and instructive articles regarding its pharmacology, mode of action and therapeutic uses.

From time to time attention has been called to certain untoward effects from the use of this drug, and it is not considered amiss at this time to emphasize the point that this drug is not without danger, and that its indiscriminate use without a careful study of its mode of action and therapeutic limitations is to be condemned.

The chief action of ephedrine appears to be due to stimulation of the sympathetic nervous system, and the effects are similar to those of epinephrine. Ephedrine acts as a circulatory stimulant, largely due to its action on the cardiac accelerator mechanism, but if toxic doses are given, a fall in blood pressure and a depressor action on the heart muscle are noted. It appears to cause constriction of blood vessels supplied with vasoconstrictor nerves, more marked in the splanchnic area than in the limbs.

Other effects of ephedrine are inhibition and relaxation of intestinal muscles, stimulation of the uterine muscle and dilatation of bronchi and mydriasis.

Coincident with the rise in blood pressure, there is a definite increase in the cardiac rate, and occasionally various types of arrhythmia occur, particularly extrasystoles, and sometimes evidence of acute cardiac failure.

Ephedrine does not seem to be very toxic for certain animals, and the minimum fatal dose is from 100 to 145 mg. per kilogram in rats.

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The drug is effectively absorbed from the intestines or may produce its effect following subcutaneous or intramuscular injection. Solutions are stable indefinitely and are not decomposed by boiling.

Ephedrine has been used as a circulatory stimulant in Addison's disease, and its efficiency as a bronchodilator has made it a valuable remedy in bronchial asthma. Its mydriatic effects are similar but more marked than those of cocaine.

Ephedrine has certain advantages over epinephrine in that its effects are more lasting, its solution is more stable and results may be secured when the drug is given by mouth. As a result, it has become a most popular drug, particularly in the treatment of patients with bronchial asthma and hay-fever, and has replaced epinephrine in these conditions to a great extent. It is also used as a mydriatic and in spinal anesthesia as a useful agent in maintaining the blood pressure.

The fact that this drug is helpful in cases of asthma and hay-fever has become known to the layman, and as a result he frequently employs it without even consulting a physician. The sale of this drug is not surrounded by any restrictions, and it may be purchased by any one. This practice is to be deplored and may be actually dangerous for certain patients, particularly when the diagnosis of asthma is not definitely established and when cardiovascular disease may exist.

The most usually noted unfavorable symptoms have been sweating, tremor, cardiac irregularity, palpitation, general weakness and occasionally nausea and vomiting.

According to Middleton and Chen, the objective and subjective effects of ephedrine are tremor, a feeling of warmth, chilly sensations, nausea and dizziness. Others of less frequent or rare occurrence are tachycardia, restlessness, mydriasis, nervousness, headache, insomnia, dyspnea, a tired feeling and drowsiness. They noted that the time of the rise of systolic pressure after oral administration of this drug varies considerably, sometimes occurring within fifteen minutes and occasionally being delayed as long as 120 minutes, the average rise occurring in thirty-seven and a half minutes.

It seems to be the concensus of opinion that this drug is contraindicated in cases of cardiac insufficiency. Miller reported the occurrence of transitory pulsus alternans in a patient with myocardial degeneration following the use of ephedrine.

In the following case we observed signs of serious cardiac embarrassment, including pulsus alternans, marked tachycardia and cardiac decompensation after the use of ephedrine for a condition diagnosed as "asthma."

REPORT OF CASE

History.—On Nov. 14, 1927, E. O. L. presented himself at the clinic of the United States Naval Medical School complaining of palpitation, which he first noted about November 7. He was perspiring freely, especially around the forehead, had a marked tremor of the fingers, complained of weakness of the muscles of the legs, shortness of breath and cough.

He had made a trip to the Orient in August, 1927. There was a history of hay-fever during the latter part of August, 1927, which disappeared in September. The patient also said that he had had attacks of hay-fever each fall for the past ten years. He said that he had been short of breath for several weeks, and that climbing stairs or even walking fast had caused dyspnea. On Oct. 18, 1927, he drove to his camp in the mountains. On the day of his arrival in the mountains he felt fatigued, and that night he woke up with a feeling of marked breathlessness and a "smothering sensation." He felt it necessary to get out of bed and raise the window to seek relief. This attack lasted for several hours and was diagnosed by the attending physician as "asthma." Up to this time, he said that he had not noticed any irregularity of the heart; in fact, his attention had never been directed to the cardiac region. Following this acute attack, he was given some red capsules. He was informed that this was ephedrine. Following this attack, he was given forty ⅜ grain (0.0243 Gm.) capsules of ephedrine and told to take these as required for relief. He took the forty capsules during the following twenty days. At the end of this period, he came under our observation with the foregoing symptoms. He knew that his heart was beating rapidly, and that it was irregular at times.

At the time when the administration of ephedrine was begun and for the first few days thereafter, the patient felt fairly comfortable. The train of symptoms described was of gradual development, becoming progressively worse as the drug was continued.

Physical Examination.—The height was 69 inches (175.3 cm.); the weight, 205 pounds (93 Kg.); the width of the chest, 39½ inches (100.3 cm.), and of the waist at the umbilicus, 49 inches (124.5 cm.). The patient was cyanotic and was using the accessory respiratory muscles; the tonsils were rather large and showed evidence of infection; the gums were retracted around the posterior molars, and the upper molars showed extensive fillings. The eyegrounds showed slightly tortuous arteries and the disks were normal. Râles were heard at the bases of both lungs, and there was markedly impaired resonance over the base of the right lung posteriorly. The heart beat was rapid, the rate being 160 beats a minute, and the sounds were suggestive of gallop rhythm. The percussion measurements were as follows: The distance from the midline to the left border in the fifth interspace was 14 cm.; the distance from the midline to the right border in the fourth interspace was 4.5 cm. The blood pressure was: systolic, 110; diastolic, 80. There was a definite pulsus alternans.

The x-ray picture of the chest taken at a distance of 2 meters shows a dilated, decompensated heart and an effusion at the right base extending upward to the sixth rib (fig. 1). The prominence of the lung markings indicate pulmonary congestion. The cardiac measurements were as follows: The distance from the midline to the left border in the fifth interspace was 15 cm.; the distance from the midline to the right border in the fourth interspace was 4.5 cm. The transverse diameter of the heart was 19.5 cm. and the transverse diameter of the chest 30 cm. This plate was taken at the time of the first examination.

Figure 2 shows the electrocardiogram taken on the same day. It indicates a cardiac rate of 160 beats a minute and shows the tachycardia to be of nodal origin. The blood picture was normal; the urine showed a specific gravity of 1.032 and albumin.

The administration of ephedrine was discontinued; the patient was put to bed, and tincture of digitalis was administered by mouth in doses of 1 cc. four times a day. The dosage was reduced to 1 cc. three times a day at the end of eight days, and was finally discontinued as the patient showed evidence of digitalization.

The cardiac rate gradually slowed, and the acute symptoms subsided. The patient, however, continued to show pulsus alternans for the following three weeks.

Fig. 1.—Dilated, decompensated heart with effusion on the right side of the chest (plate taken after the patient had continued the use of ephedrine for twenty days).

On December 3, the electrocardiogram (fig. 3) showed a cardiac rate of 110 beats a minute, a normal rhythm and a left-sided preponderance. The T waves were inverted as a result of the administration of digitalis. It is of particular interest to compare this electrocardiogram with that in figure 2, noting that the P wave has resumed its normal position, that the amplitude of the QRS complex has been increased and that a definite left-sided preponderance is apparent.

The patient continued to show steady clinical improvement. On Dec. 10, 1927, an x-ray picture of the chest (fig. 4) taken at a distance of 2 meters showed that the effusion had entirely disappeared from the right side of the chest. The fields at the bases of the lungs had resumed their normal appearance, and the shadow of the heart showed a return toward normal. The cardiac measurements were as follows: The distance from the midline to the left border in the fifth inter-

space was 12.5 cm.; the distance from the midline to the right border in the fourth interspace was 4.5 cm.; the transverse diameter of the heart was 17 cm. and the transverse diameter of chest 30 cm.

The electrocardiogram taken at this time (fig. 5) showed a cardiac rate of 88. The T waves showed definite inversion in all leads, indicating digitalization. The patient was somewhat nauseated on this day, and the administration of digitalis

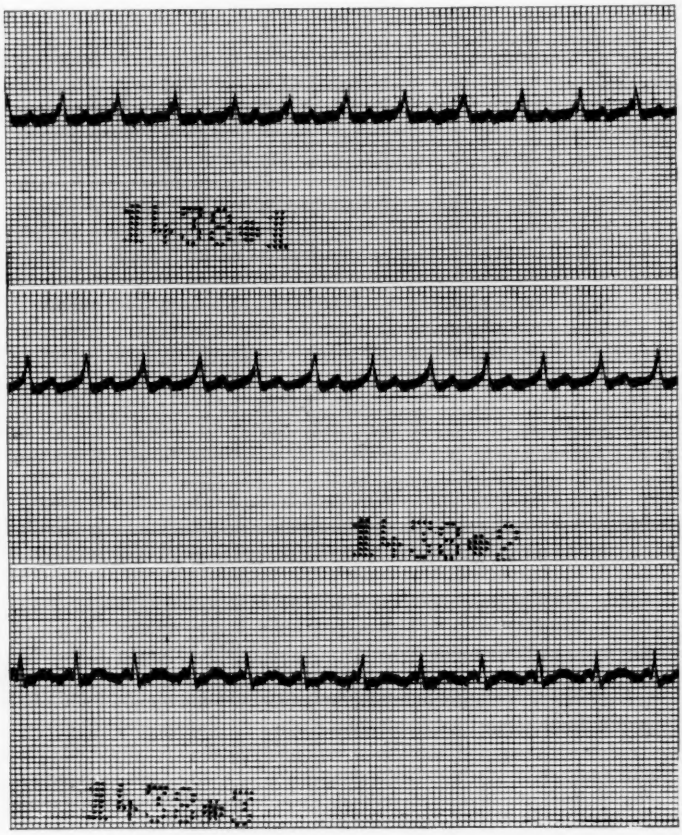

Fig. 2.—Electrocardiogram taken same day as the x-ray of the heart shown in figure 1; nodal tachycardia, with cardiac rate of 160 beats a minute.

was discontinued. The rhythm was normal, and the amplitude of the QRS complex had still further increased. The evidence of left-sided preponderance was more marked, and cardiac compensation was well established. The patient was up and about and showed none of the distressing subjective symptoms noted at the outset. The urine showed a specific gravity of 1.022 and no albumin, sugar or casts.

Examination following the patient's convalescence revealed signs of myocardial damage as evidenced by cardiac hypertrophy and lessened cardiac reserve. He continued to show shortness of breath on exertion, and following an active day invariably exhibited some edema of the ankles, so that it was necessary to keep his activities within the range of his cardiac reserve power.

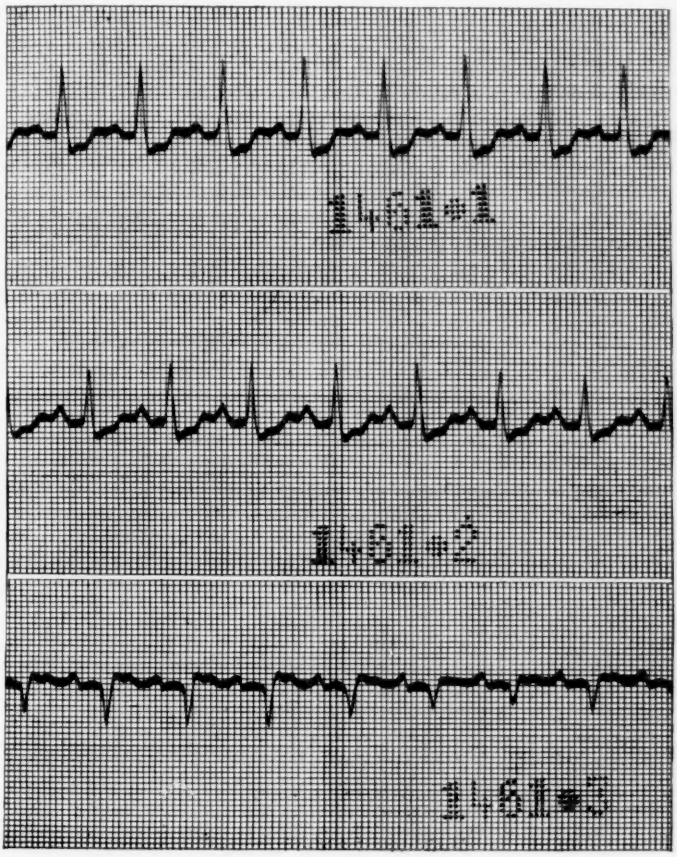

Fig. 3.—Electrocardiogram showing cardiac rate of 110 beats a minute; normal rhythm; left sided preponderance; inversion of T waves indicative of the effect of digitalis.

It was considered advisable to begin again the use of digitalis in moderate doses in order to maintain the cardiac reserve.

The patient was kept under close observation in order to detect evidence of asthma, and he did not exhibit any evidence of this condition or any signs or

symptoms of nodal tachycardia. There was no return of palpitation, sweating, tremors or any of the phenomena noted at the outset.

Pulsus alternans disappeared following the return of cardiac compensation.

It may be of interest to note that, as is usually the case, the electrocardiogram gave no indication of pulsus alternans at any time during the course of the disease, although this phenomenon was easily demonstrated by the sphygmomanometer.

It appears to be well demonstrated that the patient did not have bronchial asthma. There was no eosinophilia, and there was only a single paroxysm of dyspnea which occurred at night following a

Fig. 4.—Twenty-six days after beginning digitalis medication and discontinuance of ephedrine; the lung fields have resumed a normal appearance and the cardiac shadow shows a return toward normal.

fatiguing day. There had been evidence of a failing myocardium for several weeks preceding this attack, and there had been no return of any symptoms suggesting bronchial asthma either during convalescence or following recovery. The clinical course and marked improvement under rest and digitalis therapy would seem sufficient to establish the diagnosis of cardiac failure.

SUMMARY AND CONCLUSIONS

A clinical case is presented in which the diagnosis of asthma had been made following an acute attack of dyspnea coming on at night after

a long, fatiguing trip. The patient had been given ephedrine, ⅜ grains, and took forty doses during a period of twenty days, a total of 15 grains (0.972 Gm.). Following the administration of this drug, he developed evidence of acute cardiac decompensation accompanied by marked dyspnea, sweating, tremors, weakness and palpitation. He developed a

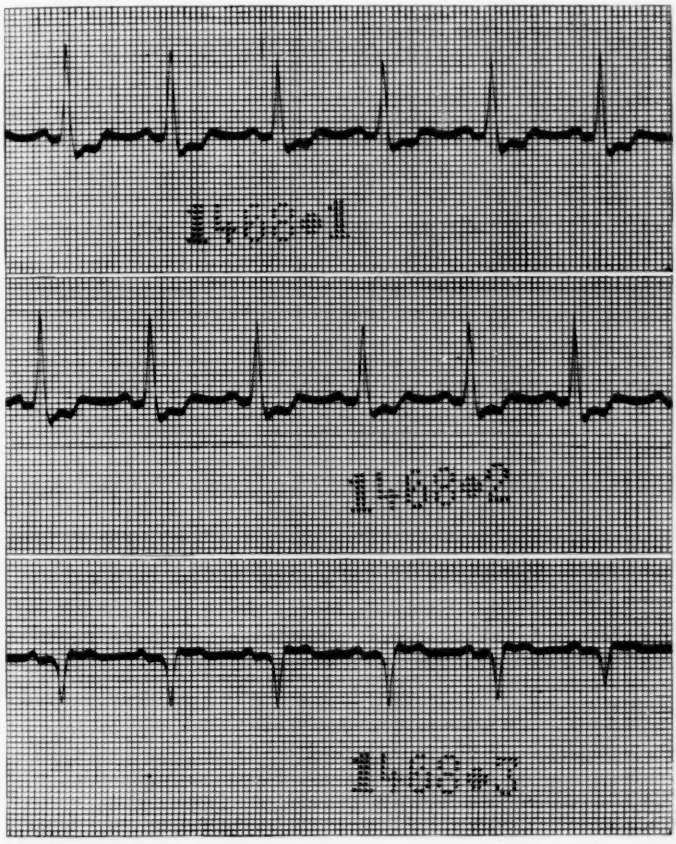

Fig. 5.—Electrocardiogram taken same day as the x-ray of the heart shown in figure 4; cardiac rate, 88; tracing characteristic of digitalization; left sided preponderance becoming more marked.

cardiac rate of 160 beats a minute, and the electrocardiogram revealed tachycardia of nodal origin. He exhibited pulsus alternans during this period of decompensation, and developed a large right pleural effusion. During the period that the patient was taking ephedrine, his condition

grew worse, and he said that following each dose of the drug the tremor, sweating and discomfort increased.

Following the discontinuance of ephedrine and the use of digitalis in adequate doses, accompanied by complete rest in bed, he showed steady improvement, the pleural effusion disappeared, and he returned to a comparatively normal state in a short time.

The serious nature of the effects of this drug would seem to justify a report on this case in order that more caution be urged in guarding against such effects in the future.

This case appears to bear out in all respects the observations of other observers regarding the danger of using ephedrine in treating patients who have damaged hearts. We believe that before ephedrine can be safely administered, the patient should be subjected to a careful examination of the cardiovascular system in order to determine whether disease of this system exists and whether or not the drug is contraindicated.

This case also illustrates the not uncommon mistake of diagnosing so-called "cardiac asthma" as true bronchial asthma. Furthermore, it shows that even in patients who exhibit signs of true bronchial asthma, a careful examination of the heart is indicated. When evidence of cardiac damage exists, ephedrine should be used with extreme caution; if any evidence of toxic symptoms develops the drug should be discontinued promptly.

We also feel that attention should be called to the fact that while this drug is highly extolled and widely exploited at present, the physician does not necessarily have to prescribe it and may make use of the other well known remedies for bronchial asthma. The following conclusions appear to be justified:

1. Ephedrine is a dangerous drug to use when patients show evidence of cardiac damage.

2. Extreme care is necessary in the diagnosis of bronchial asthma, as not infrequently cases of so-called "cardiac asthma" are put in this group.

3. Ephedrine may produce acute cardiac decompensation and pulsus alternans in patients with damaged hearts.

4. If during the administration of ephedrine the patient exhibits any toxic symptoms such as palpitation, tachycardia, arrhythmia or vasomotor disturbances, the drug should be promptly discontinued.

5. Pulsus alternans does not have the serious significance for patients who exhibit this condition with tachycardia as it has for persons with a normal cardiac rate.

6. The sale of ephedrine to the layman should be discouraged, and even its indiscriminate use by the physician is to be deplored.

SEPTICEMIA DUE TO A STRAIN OF THE BACILLUS MUCOSUS-CAPSULATUS GROUP IN A CASE OF DIABETES MELLITUS*

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AND
WILLIAM W. BEATTIE, M.D.
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The occurrence of septicemia from infection with *Bacillus mucosus-capsulatus* is not generally recognized on this continent. In France, especially among the physicians of Paris, cases have been reported at infrequent intervals. In his thesis in 1917, Colombe [1] collected sixty cases from the world's literature. Of these sixty, only twenty-five were diagnosed during life by a positive blood culture.

In 1924, Caussade, Joltrain and Surmont [2] collected fifteen new cases that had been reported since 1917, and added one of their own. Since then, additional cases have been reported by Creyx [3] and by Lereboullet and Pierrot.[4]

The present report is that of a case of *Bacillus mucosus-capsulatus* septicemia which was proved during life by two blood cultures and which terminated in death. Autopsy was not obtained.

REPORT OF CASE

History.—R. C. M., a man, aged 55, was admitted to the Royal Victoria Hospital on April 10, 1927, complaining of general malaise and soreness in the left hip joint. Seven weeks before admission, after he returned from an automobile ride, a slight chill had developed. This was followed by chilly sensations for the next few days. For about five weeks he had suffered irregularly from "indigestion" with belching of gas after meals. These symptoms were also associated with infrequent attacks of dull pain in the left hip joint, which radiated to the knee and calf muscles of the left leg; the pain disappeared with rest.

One week previous to admission, a general feeling of malaise developed, which continued until April 9, when a physician was consulted, who reported a temperature of 101 F. The next day the temperature was 104 F., and the general malaise and weakness were more marked.

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1. Colombe, J.: Les septicémies pneumobacillaires, Paris Thèse, 1917, no. 29 de la bibliothèque de la Faculté de Méd. de Paris.

2. Caussade, G.; Joltrain, E., and Surmont, J.: Septicémie à pneumobacille de Friedländer, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:148 (Feb. 8) 1924.

3. Creyx, M.: Sur un cas de pneumobacillémie, Compt. rend. Soc. de biol. **94**:596 (March 12) 1926.

4. Lereboullet, P., and Pierrot, M.: Un nouveau cas de septicémie à pneumobacille de Friedländer terminée par la guérison, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:128 (Feb. 10) 1927.

Diabetes mellitus had been present since May, 1912, the onset being associated with typical symptoms. Since September, 1921, freedom from glycosuria had been maintained through dietetic control. With the present infection, glycosuria became constant.

Examination.—The patient was a rather overnourished man, who appeared anxious and ill. The temperature was 104.8 F., the pulse rate, 100 and respirations, 28. The throat was not inflamed, and the pupils were equal and active. There was no general glandular enlargement. The lungs were normal except for an occasional moist râle at the bases. The pulse rate was regular, and the vessel wall was not palpable. The heart was normal and the blood pressure was: systolic, 140, and diastolic, 65 mm. of mercury. The abdomen was normal.

The urine was acid, of a good specific gravity, and contained albumin and sugar. There was no acetone. The microscopic examination showed hyaline casts and a few red blood cells. The blood count showed 4,800,000 red cells and 90 per cent hemoglobin. White cells counts ranged from 7,500 to 9,000 per centimeter on four occasions. The stool was negative, except for an acid reaction.

On admission, the blood urea was 0.32 Gm. per liter and the plasma carbon dioxide (capacity) was 50 per cent by volume. On April 15, the former was 0.60 Gm. per liter.

Roentgenograms of the pelvis and of both hip joints did not indicate the cause of the pain in the left hip joint.

Two Widal reactions of the blood were negative for *Bacillus typhosus* and *Bacillus paratyphoid* A and B. Two blood cultures (April 10 and 15) and one stool culture yielded large numbers of a gram-negative, nonmotile bacillus, which proved to be a member of the *Bacillus mucosus-capsulatus* group.

Subsequent Course.—The infection ran a rapid course, as will be seen from figure 1, death taking place on the seventh day after admission. Hyperglycemia, which was little affected by insulin, persisted. There was no ketonuria. Each evening, commencing on April 12, there was a severe chill associated with a rise in temperature. During the last day of life there was moderate abdominal distention with diffuse moisture in both lungs, although definite areas of consolidation did not develop. Mental stupor and unconsciousness then appeared, persisting until death.

MORPHOLOGIC AND BIOCHEMICAL CHARACTERISTICS OF THE STRAIN OF BACILLUS MUCOSUS-CAPSULATUS (KLEBSIELLA)

Bacteriologic Report.—The organism isolated on two separate occasions from the blood and once from the stool showed the following morphologic and biochemical characteristics.

It was a gram-negative, short, stout rod, nonmotile and capsulated. The capsules were easily demonstrated in cultures grown in beef infusion broth, beef infusion agar, and even in peptone water (fig. 2). On beef infusion broth, a uniform turbidity was soon produced, with a viscid creamy white ring and some sediment; later the culture became viscid. On an agar slant, the growth was creamy white, moist, raised, glistening and viscid. Gelatin was not liquefied. Litmus milk was acidified, coagulated and the litmus was reduced. The following carbohydrates were fermented, with the production of acid and gas: dextrose, mannose,

galactose, levulose, arabinose, xylose, rhamnose, mannitol, dulcitol, sorbitol, glycerol, maltose, lactose, sucrose, raffinose, inosite and salicin. Inulin and dextrin were not fermented. In peptone water after forty-eight hours, no indol was detected, but on two occasions, after incubation for nine days, a faint trace of indol was detected by Ehrlich's test (parabenzaldehyde). In nitrate broth, the nitrate was reduced to nitrite. The Voges-Proskauer reaction was positive.

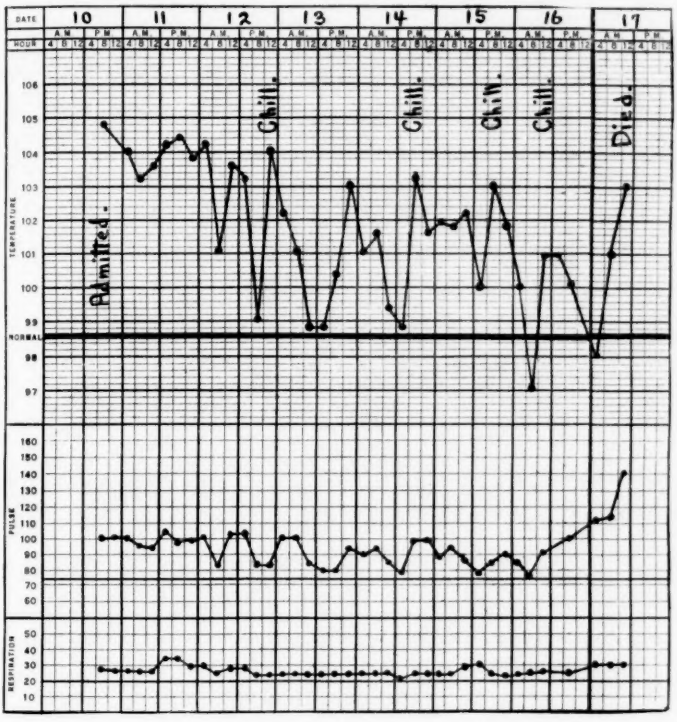

Fig. 1.—Chart showing the temperature, pulse rate and respiration throughout the course of the infection.

PATHOGENICITY

As small a dose as 0.5 cc. of a 1 : 100 dilution of a saline suspension of a twenty-hour growth on an agar slant, injected into the peritoneal cavity, killed a mouse in thirty-six hours. Larger amounts of the dilution killed five other mice more quickly.

Also an intraperitoneal injection of 0.25 cc. of a twenty-hour broth culture killed two mice in five hours and two others within ten hours. Smaller amounts killed four mice within twenty-five hours. The peri-

toneal cavity contained a mucoid exudate, with polymorphonuclear leukocytes and gram-negative capsulated bacilli.

Subcutaneous injection of 0.1 cc. of a twenty-four-hour broth culture into the abdominal wall of a mouse was followed by a localized swelling, which was covered by a scab within five days and finally disappeared. Two tenths of a cubic centimeter of the culture injected in the same way into another mouse caused death on the fifth day. Autopsy revealed a phlegmonous swelling of the abdominal and thoracic walls; of the skin, subcutaneous tissue, muscle and peritoneum; and the peritoneal cavity contained a mucoid exudate the same as has been described. Histologic examination of the lesion in the abdominal wall showed dense infiltration of the subcutaneous tissue, muscle and peritoneum with an exudate of polymorphonuclear leukocytes, fibrin and serum, and enormous numbers of bacilli (fig. 3).

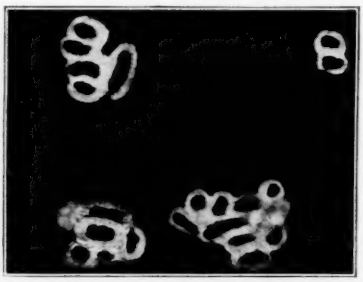

Fig. 2.—Eighteen hour culture on plain nutrient agar stained with carbol fuchsin and nigrosin showing capsules.

Five tenths cubic centimeter of the same twenty-four-hour broth culture was injected into the peritoneal cavity of a guinea-pig of about 300 Gm., and it was found dead in eighteen hours. The peritoneal cavity contained an exudate similar to that described, but no other gross lesions were noted.

The same twenty-four-hour broth culture (0.25 cc.) was injected into the subcutaneous tissue of the abdominal wall of another guinea-pig; the animal remained lively and apparently well. An indurated swelling developed which subsequently ulcerated. On the ninth day, the ulcer was covered by a scab. Slight pressure caused a small drop of creamy white pus to exude. An organism identical with the original was isolated in pure culture from this pus. Eventually, the ulcer and induration were replaced by a small scar, complete recovery having taken place.

From all sixteen animals that died from inoculation, an organism identical (so far as tested) with the original was isolated from the heart's blood.

Of nine mice inoculated by instilling 0.1 cc. of a twenty-hour broth culture into the nostrils, six died within seven days, and from five of these an organism identical with the original was isolated from the heart's blood.

In two of these animals, smears from the surface of the brain showed numerous gram-negative capsulated bacilli, morphologically identical with the original, also polymorphonuclear leukocytes. Paraffin sections of the brain of one of these showed that in the white matter there were numerous small abscesses containing leukocytes, and clear spaces filled, evidently, with serous material, and containing numerous gram-negative capsulated bacilli. Some of these abscess cavities communicated with the meninges, in which a similar exudate was found.

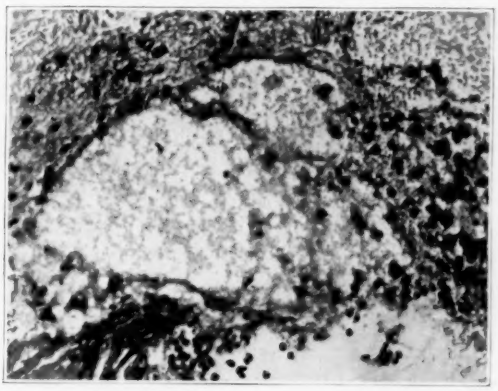

Fig. 3.—Phlegmonous infiltrated thoracic wall of a mouse showing the organisms in enormous numbers.

In one of these two animals there was an abscess about 0.6 cm. in diameter in the left side of the neck, filled with creamy white mucoid pus. Microscopic examination of this abscess showed a central mass of exudate; polymorphonuclear leukocytes, fibrin and serum with numerous gram-negative capsulated bacilli, surrounded by a wall of granulation tissue, which infiltrated the surrounding lymph nodes and lobules of the salivary glands. It appeared impossible to be sure whether the abscess primarily arose in a lymph node or in a salivary gland. An organism identical with the original was isolated from the abscess.

So far, attempts to infect guinea-pigs by instilling cultures into the nostrils have been unsuccessful.

A mouse, into the peritoneal cavity of which was injected 0.5 cc. of saline suspension of the strain of organism isolated from the stool of

the patient, was found dead on the third day. The peritoneal cavity contained an exudate identical with that described in the other animals and, besides, three grayish-white nodules were found in the spleen, in the right kidney and in the liver. Paraffin sections of these nodules revealed abscesses similar to those already described, and showed the bacilli in enormous numbers. An organism identical with the original was isolated from the heart's blood of this mouse.

BACTERIOLOGIC CONCLUSIONS

The morphology, especially the capsule formation and mucoid growth, the biochemical reactions and its pathogenicity would place this organism in the *Bacillus mucosus-capsulatus* group (genus *Klebsiella*), except that it is "Voges-Proskauer" positive and that it ferments lactose. (However, the fermentation of lactose by organisms of this group is irregular.) The positive "Voges-Proskauer" reaction allies it to the *Bacillus aerogenes-cloacae* group (*Aerobacter*), and in suger fermenting ability it corresponds to *Aerobacter oxytocum*, which differs from *Aerobacter aerogenes* in being dulcitol positive. It would seem best to consider it, at least temporarily, as a variant of the *Bacillus mucosus-capsulatus* group.

Three references to members of the *Bacillus mucosus-capsulatus* group giving a positive Voges-Proskauer reaction have been found in the literature.[5] Investigation of this point in available strains is being undertaken.

CLINICAL CHARACTERISTICS OF THE INFECTION

On admission of the patient to the hospital, it was suspected that the infection was that of typhoid fever. Against this diagnosis was the rapid onset and the rise of the fever without the usual mental torpor and dulness. Rose spots did not develop, the spleen was not palpable, and there was no leukopenia. Subsequently, the Widal reaction as well as the blood culture for *Bacillus typhosus* was found to be negative, and the appearance of the daily chill was atypical.

This case followed the usual course as reported in many cases of *Bacillus mucosus-capsulatus* septicemia. As emphasized by Creyx, there was no localization, the temperature was of the septic type, and no point of entrance was discovered.

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5. Simonds, J. P.: A Curious Accident due to Fermentation Caused by B. Pneumoniae, J. Bact. **2**:245 (May) 1917. Hewlett, R. Turner: A Manual of Bacteriology, Clinical and Applied, New York, The Macmillan Company, 1921, p. 413. Edwards, Philip R.: The Relation of Encapsulated Bacilli Found in Metritis in Mares to Encapsulated Bacilli from Human Sources, J. Bact. **15**:245 1928.

In 1912, Brissand [6] when reporting fifteen cases of septicemia due to *Bacillus mucosus-capsulatus* stressed the gravity of the infection, the constancy of pulmonary manifestations and the tendency to hemorrhages. That the infection may not terminate fatally can be justly assumed from Lereboullet and Denoyelle's [7] report of two cases in children, aged 12 and 14, who recovered. In both instances, the diagnosis was proved by blood culture. Lereboullet and Pierrot [4] have also reported another proved case in a child of 13 years, in whom recovery took place.

In certain instances the infection has assumed pyemic characteristics resulting in abscesses of the kidney, liver and spleen, and not infrequently in gross-intestinal ulceration.

Urine and Blood Data

	Intake, Gm.			Insulin Units			Urine			Blood		
										Sugar Percentage		Carbon Dioxide Capacity, per Cent by Volume
Date, 1927	Protein	Fat	Carbohydrate	A. M.	N.	P. M.	Volume, Cc.	Dextrose, Gm.	Acetone	Before Eating	After Eating	
April 10	50	100	50	..	..	..	430	3.8	0	0.324	.....	50
April 11	50	100	50	..	..	..	2,050	13.7	0	0.218	0.246	47
April 12	50	100	50	7	..	10	1,300	25.2	0	.....	0.230	
April 13	23	54	36	5	5	10	940+	12.1	0			
April 14	34	77	39	10	5	15	1,400	16.8	0	0.327	0.318	49
April 15	50	125	100	15	10	15	1,650	11.5	0	0.329	0.330	
April 16	..	...	45	15	15	15	550+	3.1	0	0.315		
April 17	..	...	10	5	..	..	Lost					

THE DIABETIC STATE

That the infection caused an exacerbation of the diabetic condition is evident. No degree of acidosis developed, but the blood sugar showed little response to insulin therapy as is usual with infection. The persistent hyperglycemia probably worked deleteriously on the course of the septicemia. These data are shown in the table.

SUMMARY

1. A case of septicemia due to a member of the *Bacillus mucosus-capsulatus* group giving a positive Voges-Proskauer reaction is reported.

2. The portal of entry of the infecting organism was undetermined. The infection ran a rapid, septic course terminating fatally without localization.

3. The case was complicated by the presence of diabetes mellitus.

6. Brissand, H.; Cordier, V., and Badolle, A.: La pneumonie à pneumobacilles, Lyon méd. **118**:817, 1912.

7. Lereboullet, P., and Denoyelle, L.: Deux cas de septicémies graves à pneumobacille de Friedländer terminées par la guérison, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:226 (Feb. 29) 1924.

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS *

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In 1921, I had the opportunity to study a patient with a pathologic condition to me entirely unique. At that time, I did not succeed in finding similar cases reported in the literature. I was at a loss to give a satisfactory name to the condition or disease, and so did not place it on file in the literature. Recently, in a report of a meeting of the Association of Physicians of Great Britain and Ireland, held May 29, 1925, I saw a brief notice of an entirely similar case, reported by F. Parkes Weber, and subsequently read his report in the *British Journal of Dermatology and Syphilis*.[1] The name he used intrigued me; now, with a title for my report, it seemed appropriate to present my observations before the Association of American Physicians, which furnished a model for the society before which Weber made his report.

The name used by me, febrile relapsing nodular nonsuppurative panniculitis, is descriptive of the process. I have added "febrile" to the terminology that Weber used to emphasize a feature which is striking and the one most likely to arouse the interest of the internist. There is fever in recurring attacks or relapses; there is inflammation of the pannicle, or panniculus adiposus, nodular in distribution and nonsuppurative; the paniculitis results in localized atrophy of the panniculus adiposus, subsequently causing a depression in the contour of the skin and giving a marked appearance of scarring. The patient is seriously sick. The cause of the inflammation remains unknown. In my study, blood cultures and cultures from the nodules were sterile. Organisms could not be found in excised tissue. In my patient, leukocytosis did not accompany the febrile periods. Histologically, in a healing lesion excised in 1920, I found in places edema and necrosis of the fat tissue, edema of the connective tissue between fat lobules, and a focal infiltration between the fat cells and in the connective tissue septums of lymphoid cells, plasma cells, young connective tissue cells, endothelial cells phagocytic for fat droplets, a few polymorphonuclear leukocytes and a rare foreign body giant cell, so that much of the subcutaneous adipose tissue thus was infiltrated. Fatty acid crystals were not present. Blood vessels, as a rule, were normal. A few showed periarteritis; rarely one showed endarteritis with proliferation of the endothelial cells.

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* Reported at a meeting of the Association of American Physicians, Washington, D. C., May 3, 1928.

1. Weber, F. Parkes: Brit. J. Dermat. **37**:301, 1925.

The inflammatory process did not extend to the dermis, and so the skin itself was not scarred. No organisms were seen. The process is well shown in the accompanying photomicrographs (figs. 1 to 7), which will serve in place of a more detailed verbal description.

Fig. 1.—Low power magnification of area of panniculus adiposus in a case of "relapsing febrile nodular nonsuppurative panniculitis."

REPORT OF A CASE

History.—A single woman, aged 25, was admitted to the Peter Bent Brigham Hospital on Feb. 5, 1921, for observation. She was of native American stock, intelligent, a college graduate and a chemist. She had never been in the tropics. The family history was negative. She had had mumps and whooping cough in

childhood, and scarlet fever at the age of 12, followed by otitis media. Her disease first appeared in 1918 with a lump under the skin of the right upper arm, followed in six months by a similar lump over the left scapula. In 1919, many lumps, described as of pea to lemon size, appeared over both lower legs. They developed in a short time. At first they were reddened, and the patient believed they were associated with some diffuse swelling from the middle of the tibia to the

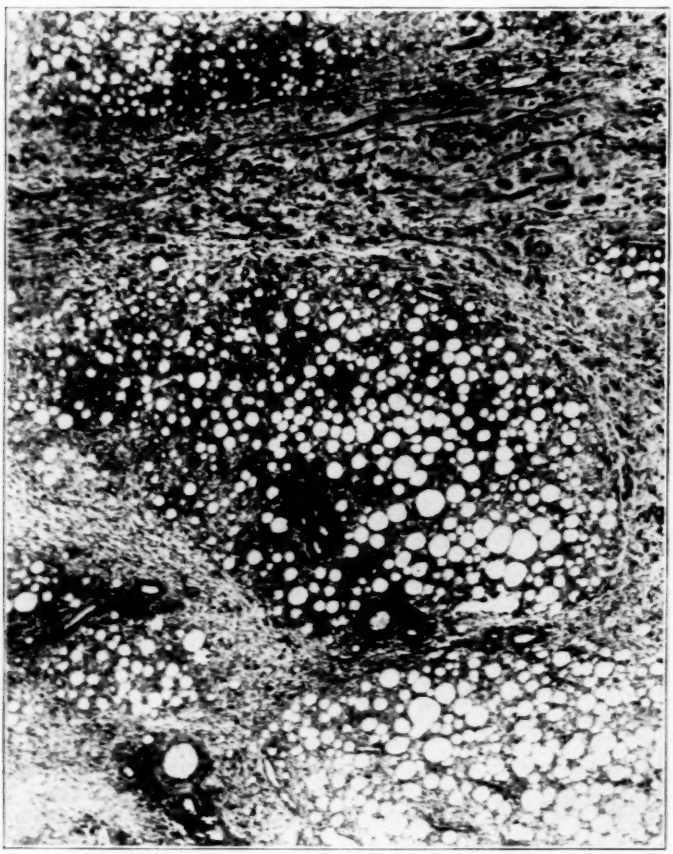

Fig. 2.—Low power magnification of area of panniculus adiposus showing marked inflammatory infiltration.

ankle. A month after the appearance of the nodules on the legs, she began to have fever associated with headache, nausea, vomiting and muscle pain. The fever fluctuated daily, but the time of highest temperature was not constant each day. For a time these variations of temperature reached a daily higher level, and then lessened each day until the normal again was reached. Defer-

vescence lasted longer than the rise. During the course of fever, other lumps might appear. The lumps would gradually flatten out, seem to attach themselves to the skin and finally leave a depression. After the temperature returned to normal, the patient felt well for four months. Then in the course of two to three weeks at least fifty new lumps appeared, with fever, chilly sensations, nausea and vomiting lasting about one month. In this attack only the

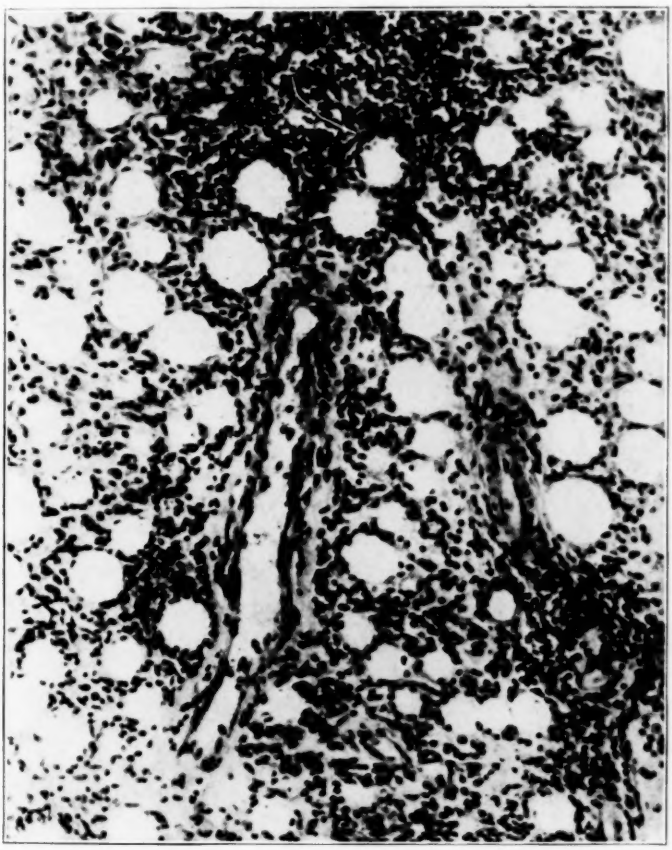

Fig. 3.—High power magnification, showing cellular infiltration of fat and connective tissue. There is evidence in places of replacement of fat by young connective tissue.

face, right forearm, palms of the hands and soles of the feet were spared. There was an interval of one month; then the third attack began and lasted for five weeks. A fourth attack occurred nine months later, in June, 1920, and lasted for a month (fig. 9 shows the fever curve in the latter part of this attack). After an interval of two months, a fifth attack developed. This was the most severe one

to date (fig. 10 shows the fever curve) and, in addition to previous symptoms, was accompanied by a slight dry cough with a "catch" over the lower sternum and slight jaundice for one day. Fever persisted for over five weeks. Between the fourth and fifth attacks the patient felt continuously tired. The sixth attack began on Jan. 24, 1921 with chills, fever and a dry cough. In this attack, she entered the Peter Bent Brigham Hospital on Feb. 5, 1921.

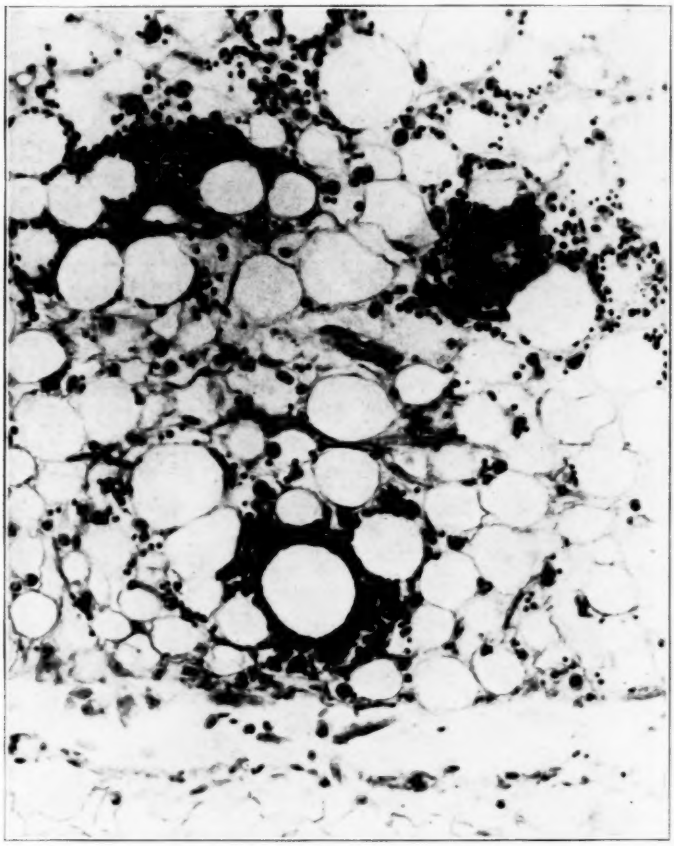

Fig. 4.—High power magnification, showing cellular infiltration of fatty tissue and a few macrophages.

Examination.—With the exception of the observations made on the subcutaneous tissue, the results of the physical examination were negative. Laboratory examination revealed: urine normal; hemoglobin, 85 per cent; red blood cells, 4,929,000; white blood cells, 3,000. The differential count showed: polymorphonuclears, 55 per cent; lymphocytes, 45 per cent. Five days later, there were 4,200 white cells; 50 per cent polymorphonuclears, 47.5 per cent lymphocytes

and 2.5 per cent large mononuclears. Six days later, the white cell count was 6,100. The Wassermann reaction was negative. The blood culture on Feb. 6, 1921, did not show any growth (on June 15, 1920, and on Nov. 11, 1923, blood cultures did not show growth). The basal metabolic rate was —12 per cent. Figure 11 shows the fever curve of this, the sixth, attack. Cultures made from the nodules on Nov. 11, 1923, were negative.

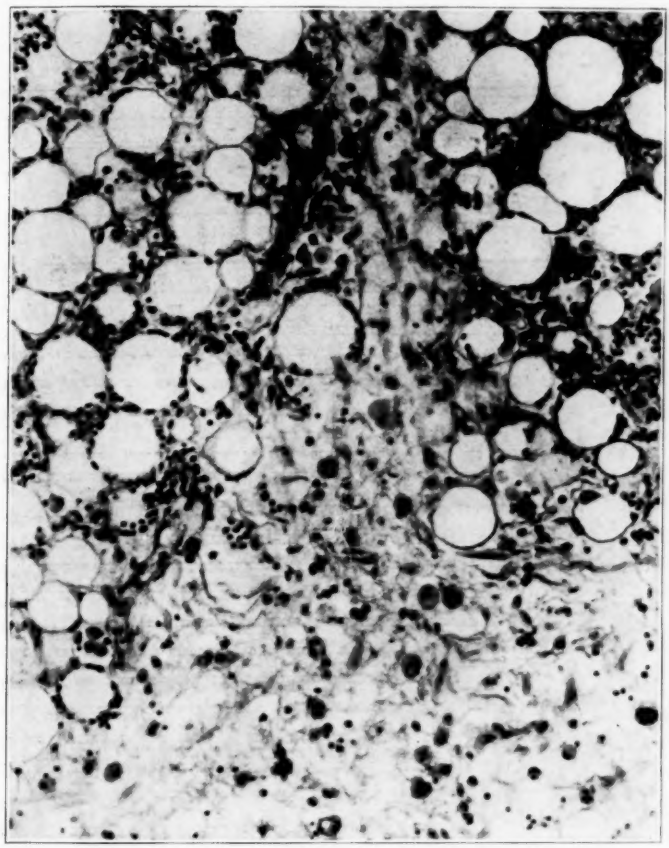

Fig. 5.—High power magnification, showing more macrophages and an area of edematous connective tissue.

Clinical Observations.—The skin condition (sixth attack) was described at the time by me as follows: "The striking thing, seen at first glance, are deep, irregular depressions in the cutaneous surfaces, distributed as will be described, not symmetrical in distribution and usually without color change in the skin (fig. 8). There is no local heat. The left lower leg shows, as the most striking phenomenon, an unsymmetrical contour due to irregular depressions with intervening slight

elevations, more marked between the middle of the tibia and the knee than below, and rather more marked on the external than on the internal surface. Over the region covered by the anterior surface of the tibia, just above the mid-point, there is a definite swelling with ill defined margins, measuring 5 by 7 cm., the middle slightly reddened, being a dull, pale red, that almost disappears under pressure, leaving a slightly pale brownish background. This area does not pit on pressure.

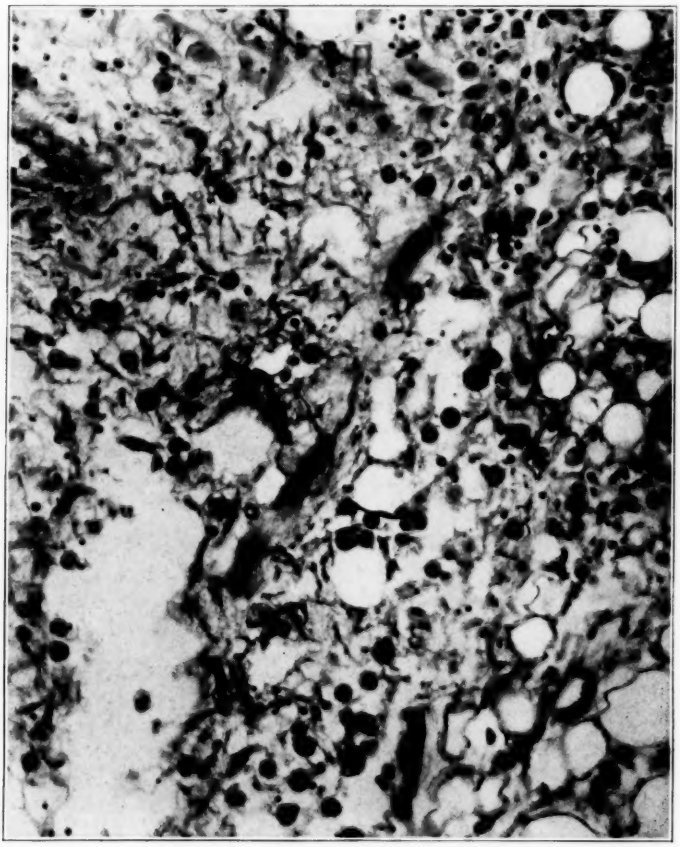

Fig. 6.—Similar to figure 5, with small area of necrotic fatty tissue at one margin.

On palpation this nodule of swelling is not of uniform consistency, but has slightly firmer portions with intervening softer portions, giving a vague sense of fluctuation. At the outer surface of this is a depression about 3 cm. in length by 2 cm. in width with indistinct margins, apparently the result of a loss of subcutaneous tissue. Just above the outer side of this depression is another slightly elevated

area about 2 cm. in diameter, rather firmer than the elevation first described. Like the first one, this is vaguely outlined, apparently shading off into surrounding normal tissue. Over these elevations the skin can not be picked up in folds as well as over the unaffected part, and much less well than over the depressed areas. The texture of the skin over all of these places seems normal, and there is no

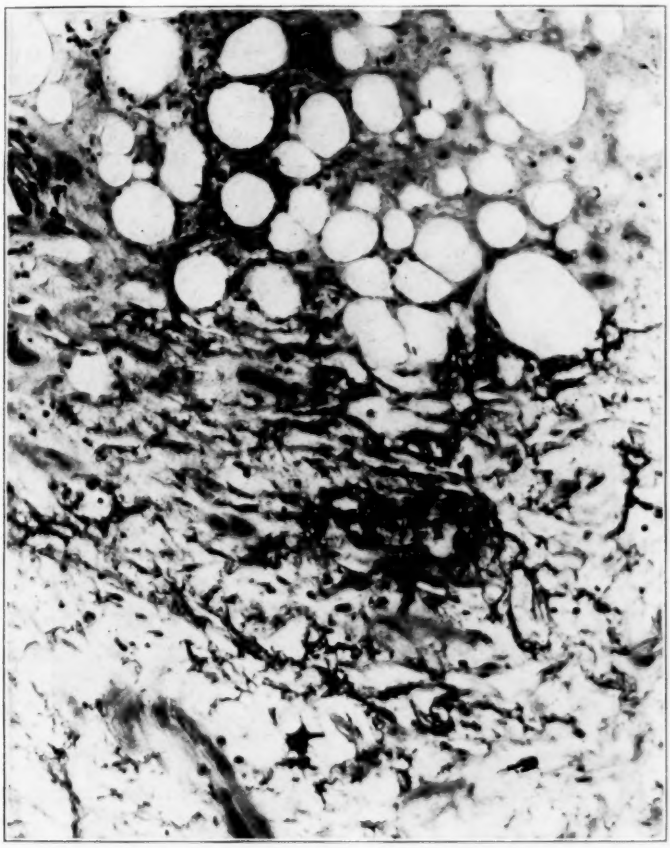

Fig. 7.—High power magnification, showing necrotic fatty tissue and an area with fibrin threads.

firm induration to be made out of either the swellings or the elevations. Over the lower half and outer surface of the leg, there seems to be considerable diffuse atrophy of the subcutaneous tissue, which leaves the surface depressed; the skin feels a trifle thickened, but may be picked up easily in folds. The skin here has a slightly brownish discoloration. This is one of the older lesions and represented at one time a diffuse uniform swelling.

"Just between these two areas, but more posteriorly on the leg, is the only lesion that has developed during this period of fever. It appeared on February 12, noticed at that time by the patient as a slight local discomfort, feeling somewhat tender and like a little nodule under the skin. This was very indistinct, and I was uncertain as to whether at this time I could make it out definitely. Two days later, there was a definite, though not very firm nodule at this point, apparently in the subcutaneous tissue, not more than 0.5 cm. in diameter. It subsequently has not increased in size. About the middle of the calf of this leg, there is a depression. Along the inner surface of the leg, there are irregularities of subcutaneous tissue, not visible swellings but areas which are felt as distinct irregularities, more

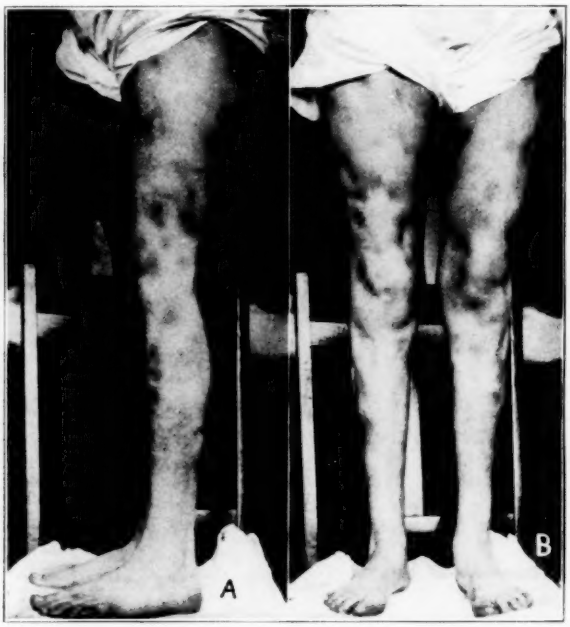

Fig. 8.—Deep irregular depressions in the cutaneous surface of the legs of a patient suffering from an attack of relapsing febrile nodular nonsuppurative panniculitis.

flattened than those already described, and feeling a bit as if the skin were attached slightly to them. To one's fingers, moving up and down the leg, they give the sensation of irregular, beaded or button-like masses not entirely separated from each other and extending in a linear arrangement. There are none of these on the dorsum or sole of the foot.

"The right leg shows a similar irregularity of contour, with depressions from 3 to 5 cm. in diameter, and intervening moderately elevated areas, as described for the other leg. Just as on the left leg, so on the posterior surface of the right leg there is a band or string of irregular nodules extending from a little below the

knee nearly to the ankle. None of these areas looks as red as those on the left leg, but the skin in places shows a slight redness and quite definite brownish discoloration. None of these masses seems attached to the deep fascia over the muscles, and they apparently are not attached to the muscles or tendons.

"On the upper right leg there are larger, similar depressions with intervening indefinite elevations. Just over the thigh region, a little anterior to the head of the femur, there are rather deep depressions. In between these are no definite nodules, but the subcutaneous tissue in places feels firmer than normal. The upper leg on the other side shows much the same picture.

"The right hand and forearm do not show any lesions. The left arm shows a depression on the forearm on the outer surface a little below the elbow. The upper right arm shows a scar slightly above the elbow where a nodule had been excised for examination, and just back of the deltoid muscle there is a very definite depression. Over the insertion of the deltoid there are vague swellings, but nowhere on the upper arm are these swellings definite or firm. The upper left arm is quite similar in general to the right. Just beneath the outer border of the left clavicle there is a deep depression, in which the subcutaneous tissue has entirely disappeared. Here the skin is not indurated, and no irregularity or thickening is felt. There have been no lesions on the neck, face or scalp. There are a scar and a depression from one of the early lesions over the middle of the left scapula. In the lower right axillary region there is a moderate depression. In the lumbar region, just over the lower right half, there is a depression 3 to 4 cm. in diameter, and at its lower border is a small, irregular nodule in the skin. On the abdomen are scattered irregular, smaller depressions with, in places, irregularities to be felt in the deeper subcutaneous tissue."

For two years the patient remained well, but in February, 1923, a seventh attack began with typical lumps developing on her legs. She kept at her work as a chemist until May 10, 1923, though during the latter part of the period she had a daily afternoon temperature of 100 F. On that date, her temperature rose to 103 F., and many new lumps appeared, chiefly on the legs, but also on the arms and back; nausea developed and she felt worn out. By June 1, this attack was over. On August 3, an eighth attack began, with many lumps and a rise of temperature to 102 F. This attack lasted two months, but thereafter the patient continued to feel bad and to ache as if she were going to have grip; her ankles felt tense, and at night were slightly swollen. I saw her again on November 7. The lesions on the skin were much as previously described; they felt firm and seemed to be in the subcutaneous tissue; they were not tender; the depressed areas were rather darkly pigmented. The ankles were red and tender, and the right felt brawny to the touch. The results of the general physical examination were negative. The blood showed: hemoglobin, 96 per cent; white cells, 3,800, and red cells, 4,992,000. The urine was normal. The patient gradually improved and was well until about the middle of July, 1924; then a ninth attack began, of the usual character and length.

After recovering from the ninth attack, the patient remained well until the latter part of November, 1927; then a tenth attack began. The character of this attack was much like that of the others and it lasted into January, 1928. Late in February, 1928, when well along in convalescence from her tenth attack, the patient developed acute appendicitis; she was operated on, and complications did not follow.

Weber's case, also that of a woman, aged 50, was observed in three attacks accompanied by fever. His description and the photomicrographs

in his report show that the conditions he observed were very similar to those observed in my case, except that the bit of tissue from his patient showed more multinuclear giant cells than that from mine. I find no other essential difference between his case and mine. Weber seems to have considered his case as possibly unique, though he believed that it should be regarded as allied to Whitfield's [2] type of erythema induratum.

In 1916, Gilchrist and Ketron,[3] under the title, "A Unique Case of Atrophy of the Fatty Layer of the Skin Preceded by the Ingestion of the Fat by Large Phagocytic Cells, Macrophages," described a girl aged 8 in Baltimore whose mother stated, in giving the child's history, that "she had had feverish attacks and loss of appetite on several occasions," and who showed changes in the legs (illustrated in the article by photographs) strikingly similar to those observed in Weber's patient and in mine. The 8 year old patient had slight fever while in the hospital. The changes were confined to the legs. Excised bits showed, on microscopic examination, appearances similar to those described by Weber and by me, changes confined to the subcutaneous fat. Looking at the illustrations and reading the descriptions of Gilchrist and Ketron, one can but feel that the condition is the same as that described by Weber and me. Weber used, too, in his title the words, "showing phagocytosis of fat cells by macrophages."

Warfield [4] has made a report of a condition under the descriptive title of "Multiple Symmetrical Gangrene of the Fat of the Abdominal Wall in a Case of Alcoholic Neuritis," which may be closely related to the disease here being described. Unfortunately, excised tissue was lost before histologic examination could be made. In Warfield's case, the subcutaneous tissue became gangrenous and the skin ulcerated; it did not in the three cases just reviewed, but there was the feature of indurated lesions in the panniculus, developing in succession.

In 1922, Lee and Adair [5] described a condition, unique in their opinion, under the title "Traumatic Fat Necrosis of the Breast," in which the tissue has some similarity in histology to the tissue from the cases under discussion here. They believed that in their patients trauma had been a causative factor, leading to necrosis of the fat tissue of the breast with subsequent cellular infiltration. Perhaps this condition bears some relation to the more generalized distribution of focal areas of inflammation of the subcutaneous fat described here.

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2. Whitfield: Am. J. M. Sc. **122**:828, 1901.
3. Gilchrist and Ketron: Bull. Johns Hopkins Hosp. **27**:291, 1916.
4. Warfield: Ann. Clin. Med. **5**:884, 1927.
5. Lee and Adair: Surg. Gynec. Obst. **34**:521, 1922.

The term panniculitis is used, too, in a somewhat different relationship, expressive of a form of chronic rheumatic disease. Stockman,[6] for example, has just published a paper under the title "Chronic Muscular Rheumatism and Panniculitis," in which he says:

> Panniculitis is a fibrositis of the panniculus adiposus, and has the same etiology and pathology as fibrositis generally. Its anatomical distribution, however, confers on it certain clinical characteristics which merit some special description. The new fibrotic tissue assumes two forms, according to its situation. Over the deltoids, shoulders, back, flank, upper abdomen, hips, and outer sides of the thighs it is dense and evenly spread, giving the skin a hard brawny feel, while on the inner surfaces of the upper arms and thighs, abdomen, and pectoral regions it is in numerous pea-like masses lying in the subcutaneous fat and often forming veritable fibro-fatty pads at the inner sides of the knees and elsewhere. The little masses can be easily felt, and are exceedingly tender on pressure, as is likewise the whole subcutaneous overgrowth. Sometimes distinct encapsulated

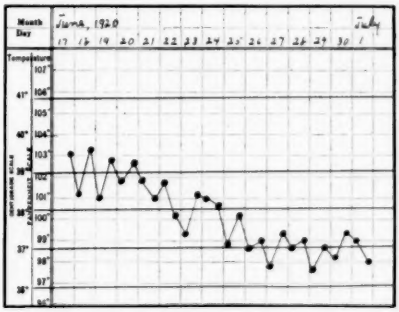

Fig. 9.—Temperature curve of the patient during the fourth attack of relapsing febrile nodular nonsuppurative panniculitis.

> lipomata are found, and these have a core of inflamed fibrous tissue, as if the local irritation had determined their growth.

He regards this as an extremely common condition. The nodular form, as described by him, has some resemblance to the condition described in the present paper and conceivably might be a mild form of it. The exact relationship of Stockman's panniculitis to acute rheumatic fever is not very clear from his paper, though he seems to think that there is some relationship.

There is another condition that may be closely related to relapsing febrile nodular nonsuppurative panniculitis, which I have seen through the courtesy of colleagues at the New England Children's Hospital.[7]

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6. Stockman: Brit. M. J. **1**:293, 1928.

7. Wilens, Gustav, and Derby, Joseph: Calcification of Subcutaneous Tissue in a Child (Calcinosus Universalis), Am. J. Dis. Child. **31**:34 (Jan.) 1926.

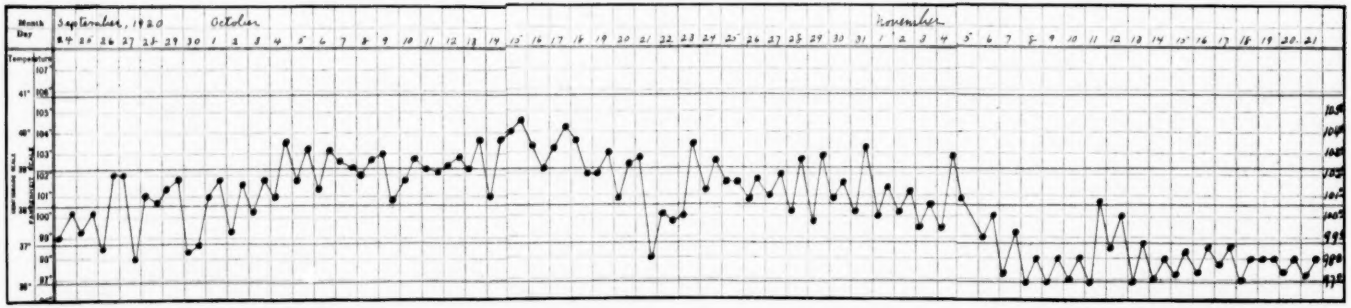

Fig. 10.—Temperature curve during the fifth attack.

In this condition areas of calcification occur in the subcutaneous fat, presumably following inflammation and necrosis. It is a question whether cases of this kind should be included. In certain respects, they seem unlike enough to be regarded, for the present at least, as of a different clinical entity. In some of the reported cases, in addition to calcification, there are changes in the tissue suggestive of those described in this paper.

The fever and relapses suggest that the condition here being reported may be a manifestation of undulant fever (infection with organisms of the mellitensis abortus group. But cultures in my case were negative, and there was no opportunity at the time of observation to test the serum for immunity reactions to fit such a hypothesis.

Possibly a more diligent search of the literature would reveal the fact that other patients have suffered from the disease represented by

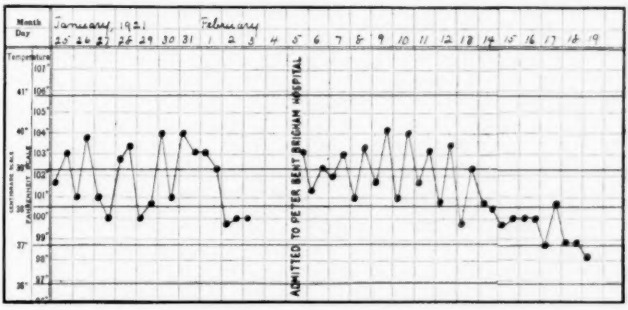

Fig. 11.—Temperature curve during the sixth attack.

the three cases of Gilchrist and Ketron, Weber, and myself. It seems to be a reasonably definite clinical entity, possibly a syndrome, rather than a disease. The severity of symptoms with fever during attacks and their repetition again and again are most notable.

SUMMARY

There is a disease characterized by recurring attacks of fever, associated with a peculiar nodular inflammation of the subcutaneous tissue. Some of the fatty tissue necroses, and much of it becomes infiltrated with lymphoid and plasma cells. Macrophages take up fat in fine droplets. A few foreign body giant cells form. There results in time atrophy of the inflammatory nodule causing a depression in the contour of the skin. Suppuration does not occur, and the continuity of the skin is unbroken. The cause of the disease is unknown. The term "relapsing febrile nodular nonsuppurative panniculitis" is descriptive of the condition.

PANCREATOGENOUS FATTY DIARRHEA

REPORT OF A CASE *

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COPENHAGEN, DENMARK

A case of pancreatogenous fatty diarrhea caused by chronic pancreatitis with extensive formation of calculi in the secretory ducts is discussed in this article. In a previous paper [1] I discussed this condition in detail; I shall now review some problems concerning the pathogenesis of the condition which were not discussed in that paper.

REPORT OF CASE

History.—A stevedore, aged 43, was admitted to the hospital on Dec. 17, 1926, and was discharged on March 13, 1927. It was said that he had been born with "scaly skin," ichthyosis; his brother and his uncle were said to have suffered from the same condition. The skin lesions, however, had improved considerably during recent years. Twenty-five years previous to admission he had been a sailor, and had visited a number of ports during a period of one and a half years, but had never been south of Algiers.

For the past twenty years, he had worked as a stevedore. Six years prior to his admission to the hospital, he had had an attack of acute bronchitis, which was followed by frequent relapses. He was admitted to the Bispebjerg Hospital in December, 1926, for an acute attack of this condition. At that time, he did not pay any attention to his main ailment, the diarrhea. The patient drank as much as ten bottles of beer a day. He said that he had not had syphilis; the Wassermann reaction was ÷. In his youth, he had had gonorrhea.

During the past five years, the patient had suffered from diarrhea; from four to five pasty, semifluid but voluminous stools were passed in twenty-four hours. The diarrhea had varied somewhat in intensity, but it had been present throughout these years. He had soon noticed that the stools were lighter than normal, being straw-colored or yellowish gray. On standing, the stool was soon covered with a greasy layer of yellow oil, which seemed to exude from the excretion; this oil hardened rapidly, and then looked a great deal like butter. Sometimes this oily mass would pass from the rectum together with the stool, and in rare instances it would pass at night also. The patient noticed that the oil was most abundant when he was on a fatty diet. Occasionally he had had some slight oppression and nausea, but complained only of a gaseous dilatation of the abdomen. He had never suffered from pain, and he could eat any kind of food without discomfort. His appetite had increased markedly with the progress of the condition. He had lost only 11 pounds (5 Kg.), in spite of an apparently large loss of fat through many years. Recently, however, he had become a little tired from working. Neither stomatitis nor icterus had ever been present.

Physical Examination.—The patient looked healthy, perhaps slightly anemic, and was fairly well nourished. The tongue was somewhat coated, and showed

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* From the Medical Department of St. Elizabeth's Hospital, Copenhagen.

* Delivered before Dansk Selskab for intern medicine.

1. Thaysen, T. E. Hess: Acta med. Scandinav. **64**:292, 1926.

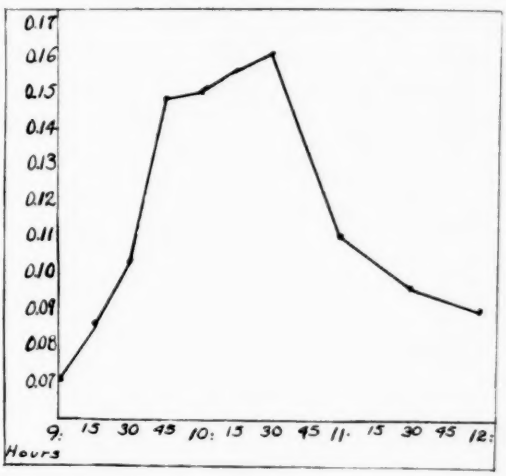
impressions of the teeth. Neither stomatitis nor glossitis was present. The organs of the neck were normal. Icterus was not present. The heart and lungs did not present any abnormality with the exception of a few rhonchi posteriorly.

The abdomen was rather large, distended, puffy and inflated, but no tumor was found in the region of the pancreas. Neither the liver nor the spleen was enlarged. Ascites was not present.

The skin was rather dry, with remnants of the condition of ichthyosis already mentioned. The patient perspired readily. He had an occipital alopecia areata.

Numerous urinalyses revealed no albumin and sugar. The basal metabolism was from 98.1 to 100.6 per cent (Du Bois-Benedict).

The stomach secretion was shown by the Ewald test meal to be 80+ 25 cc., Congo, 58/75, phenolphthalein, well chymified. There was no retention after six hours.



Blood sugar curve after ingestion of 50 Gm. of dextrose.

An examination of the blood (in Bispebjerg Hospital before admission) revealed hemoglobin, 73 per cent; red corpuscles, 3,650,000; white corpuscles, 6,800; index, 1; platelets, 298,000, and plasma color, 5. A later examination (Feb. 23, 1927) showed the following: hemoglobin, 72 per cent; red corpuscles, 4,400,000; white corpuscles, 5,000; index, 0.9. The differential blood count was normal.

Three examinations of the blood sugar curve after ingestion of from 50 to 100 Gm. of dextrose gave identical results. The curve rose to about 0.163 and fell slowly; it did not return to the starting point in three hours (chart). Sugar was not present in the urine throughout the experiment.

The stools were voluminous; as much as 1150 Gm. were passed in twenty-four hours; they were yellowish white or grayish yellow, sour and foul-smelling. On standing, they yielded a large, yellowish, butter-like mass which on examination proved to contain 87.74 per cent neutral fats; 9.77 per cent free fatty acids, and 0.24 per cent soaps (calculated as oleic acid).

Microscopic examination of the stool showed numerous droplets of fat, besides neutral fat (nile blue sulphate stain), many striated muscle fibers without nuclei, much starch, and granulose-containing bacteria; fermentation to 35 cc. in Kemp's fermentation apparatus (normally about 10 cc.).

The reaction to Schmidt's nuclear test was negative.

On Feb. 19, 1927, 1 cc. of duodenal juice was tested every 10 minutes. The results are shown in table 1.

TABLE 1.—*Results of Duodenal Test*

	p_H	Lipase*	Trypsin†	Diastase‡
Jan. 10, 1927	....	0	16.2	20.48
Feb. 19, 1927	3.44	2.4	0	0
	3.35	2.0		
	5.56	1.6		
	6.35	1.6		
	7.31	1.3		
	7.22	1.2		
	7.7	1.1	0	32

* Determined by Bondi's method.
† Determined by Gross' method.
‡ Determined by Wohlgemuth's method.

TABLE 2.—*Comparative Results of Analysis of Stools of Three Patients*

Name	Age (Years)		Feces in 24 Hours, Gm.	Elimination of Drystuff in 24 Hours, Gm.	Fat Excreted in 24 Hours, Gm.	Fat Ingested in 24 Hours, Gm.	Loss of Fat in per Cent	Nitrogen Excreted in 24 Hours, Gm.	Nitrogen Ingested in 24 Hours, Gm.	Loss of Nitrogen in per Cent	Free Fatty Acids in per Cent of Excreted Fats	Free Fatty Acids Excreted, Gm.	Soaps in per Cent of Excreted Fats	Soaps Excreted, Gm.	Neutral Fat in per Cent of Excreted Fats	Neutral Fat Excreted, Gm.
M.*	57	♂	256	27.9	9.80	250	3.96	1.6	13.9	11.5	12.4	1.25	57.5	5.68	30	2.97
V. K.†	41	♂	734	174.6	85.3	136	62.7	9.71	19.8	53.9	36.3	48.8	5.4	6.0	37.5	31.8
			734	186.9	101.12	136	74.3	9.63	19.8	48.5	57.2	36.7	5.9	4.6	57.8	58.8
V. T.‡	46	♂	1,090	262.7	132.5	95	139.5	16.8	17.6	97	65.2	87.4	5.7	7.5	29.1	38.56
			147	51	21.3	72	29.4	3.2	16	21	75.9	16.2	10.4	2.2	13.7	2.90

* M. is the patient in an unpublished report of a case of pancreatogenous fatty diarrhea in mild diabetes; on examination the digestion of fat and protein was found to be normal.
† V. K. is the patient discussed in this paper.
‡ V. T. is the architect, mentioned in this paper, whose pancreas on autopsy was found to be atrophic.

Roentgenograms of the pancreatic region showed a row of shadows, slightly larger than a pea, scattered along the course of the pancreas from the caput to the cauda. A shadow as large as a hazelnut was seen in the head of the pancreas. Cholecystography showed a normal gallbladder lateral to the shadows of the calculi.

Treatment and Course.—Immediately after admission the patient was given a test diet consisting of: 200 Gm. of rye bread, 100 Gm. of wheat bread, 75 Gm. of butter, 200 Gm. of boiled codfish, 250 Gm. of broth, 250 Gm. of potatoes, 200 Gm. of vegetables, 150 Gm. of cream, 600 Gm. of oatmeal-porridge, 50 Gm. of cheese and 3 eggs.

This diet contained 124 Gm. of albumin and 136 Gm. of fat. After the patient had remained on this test diet for five days, the stools of three days were analyzed (table 2).[2]

While the patient was on this test diet (twelve days), the total daily intake amounted to 124 Gm. of albumin, 136 Gm. of fat and 268 Gm. of carbohydrates (besides sugar in tea), amounting in all to about 2,872 calories. In the stools he lost 85.3 Gm. of fat. As a part of this fat—about 8 Gm.—is derived from the secretion of the intestinal tract, the loss of fat then was 77.3 Gm. or 724.5 calories. The daily excretion of albumin amounted to 10.7 Gm. nitrogen. As the normal excretion of nitrogen may be taken to be about 2 Gm.—chiefly derived from the intestinal secretion and the intestinal epithelium, and I take 3 Gm. to be its maximal limit—he had an additional loss of 8.7 Gm. of nitrogen corresponding to 54.3 Gm. of albumin or about 223 calories. He thus had at his disposal 2,872 — (724 + 223), or 1,925 calories; the basal metabolism (normally from 98.1 per cent to 100.6 per cent) would normally require 1,660 calories,[3] as the patient's height was 175 cm., his weight, 63.75 Kg. and his body surface, 1.75 square meters.

Thus, according to this calculation, there was a balance of 265 calories from the total supply. These calories were disposed of by bowel movements usually twice a day in the process of digestion, and by gain in weight. One would be inclined to expect only a slight gain in weight, but the patient gained 8 pounds (3.5 Kg.) in twelve days. It should be mentioned that the stools were formed or only slightly liquid during the patient's four days' stay in the Bispebjerg Hospital. The diuresis was normal, from 1,200 to 2,000 cc.

The patient gained 22 pounds (9.75 Kg.) in weight while he was being treated in St. Elizabeth's Hospital. During the last week before his discharge, he gained 1,000 Gm.; this gain was made on the same diet with the same supply of calories as that at the time of the first examination of the metabolism. The last gain could hardly be due to retention of water, although the marked gain in weight at the time of the first examination of the metabolism most likely should be attributed to retention of water. This striking faculty of utilizing food contrasts strongly with the extreme waste of proteins as well as fat with a subsequent severe loss in weight, as has been demonstrated in dogs on which pancreatectomy had been performed (Hédon,[4] Falta, Grote and Stähelin[5]). This is suggestive of the theory that the pancreas is of importance as a regulator of the metabolism by means of an internal secretion—an internal secretion which my patient, with the marked impairment of the external pancreatic function, must have preserved intact.

2. Several authors claim that an increased amount of lecithin in the stools is characteristic of the pancreatogenous steatorrhea as contradistinguished from the other forms of abnormal fat excretion, because it was thought (Deucher) that only the pancreatic juice was capable of splitting the lecithin. Apart from the fact that micro-organisms in the intestinal tract also are able to split this phosphatide, the quantitative determination of lecithin is most uncertain. For the phosphatides—especially the lecithin—are unstable compounds and are readily split. Furthermore, there are at least two kinds of phosphatides with one or two phosphorus atoms respectively; this makes it impossible to estimate these substances quantitatively by determining the amount of phosphorus. The quantitative proportion of the two phosphatides varies considerably, and consequently it can simulate an increase or a decrease of the phosphatide content.

3. Calculated as 950 calories to 1 square meter of surface.

4. Hédon and Ville: Arch. de Physiol. **9**:622, 1897.

5. Falta, Grote and Stähelin: Hofmeister's Beitr. **66**:1, 1907.

I should mention one more of the patient's symptoms, namely, mild anemia (hemoglobin 70 per cent). It has been asserted (Mayo Robson,[6] Deaver [7] and Chvosteck [8]) that pancreatic lesions often are associated with anemia; this is true in about half of Deaver's cases. Deaver came to the conclusion that the anemia is a secondary effect of lowered nutrition, while Mayo Robson and, particularly, Chvosteck maintained that the pancreatic lesion is the direct cause of the anemia, which can be of a pernicious type. In three cases of pancreatic lesion with anemia, reported by Chvosteck, one patient presented an anemia which at first was secondary but which became pernicious shortly before death. There is, however, no proof that the patient suffered from a pancreatogenous steatorrhea; his condition can just as well be considered nontropical sprue. Autopsy was performed in the other two cases; this showed that the pancreatic lesion was complicated with simple anemia. Mayo Robson likewise stated that the anemia in chronic pancreatitis can be of a pernicious type; but the evidence he gives is vague. He reported the number of red blood corpuscles as being from 3,000,000 to 3,500,000, and the hemoglobin from 50 to 70 per cent. To my knowledge, Mayo Robson does not furnish any other evidence of pernicious anemia in chronic pancreatitis. Walko reported a case of acute pancreatitis with anemia in which the index was raised, but this case was hardly one of pernicious anemia; it was probably toxic anemia combined with intensive regenerative processes in the bone marrow.

In a previous paper,[1] I discussed at greater length the question of anemia in chronic pancreatitis with fatty diarrhea. Here I merely wish to say that in the six patients with pancreatogenous fatty diarrhea whom I have examined, only two presented a condition of mild anemia, hemoglobin 77 per cent and 70 per cent (this case), and that the only other abnormality revealed by examination of the blood was a low number of platelets in one case (12,000) and a small but hardly abnormal number of platelets in another case (250,000).

Further, the exceedingly voracious appetite is noteworthy, a phenomenon which I repeatedly have observed in cases of pancreatogenous fatty diarrhea. Besides plenty of dinner, cold meats and other food the patient in the present case would eat thirty slices of bread (about 700 Gm.) a day. A similar strong sensation of hunger was observed in dogs on which pancreatectomy had been performed.

An examination of the enzyme content of the duodenal juice showed that the lipolytic enzyme is present constantly in only a slight amount, even in those tests in which the hydrogen ion concentration is most

6. Robson, Mayo: Edinburgh M. J. **18:** 1905, p. 485.

7. Deaver: New York M. J. **95:**573, 1912.

8. Chvosteck: Wien klin Wchnschr. **31:** 1918, no. 5, p. 121.

favorable to the action of lipase (p_H from 6 to 7). I did not find any similar condition in thirteen normal persons. It is not abnormal that neither tryptic nor diastatic action was observed at the low hydrogen ion concentration 3.44; but the small amount of these enzymes at p_H from 6 to 7.7 is extraordinary. A previous examination showed absence of lipase, a faint tryptic and a normal diastatic action. Thus the amount of diastase varies a great deal; the trypsin is more constant, but is present in only a slight amount; the lipolytic action is constantly low, which, I think, indicates a pancreatic lesion. At any rate, these observations agree with the results of the examination of the metabolism.

There can hardly be any doubt that the condition in this case was a typical pancreatogenous fatty diarrhea. The insidious development of the lesion without any previous symptoms from the gastro-intestinal tract, the quickly observed steatorrhea with production of a yellowish oily mass and the marked increase in appetite which explains the relatively small loss in weight, sustain the interpretation of the case. As I have shown, the three cardinal symptoms of pancreatogenous fatty diarrhea are: steatorrhea, azotorrhea and permanent or alimentary glycosuria of a diabetic type. The two symptoms first mentioned were present in this case to a marked degree, but I was not able to demonstrate glycosuria. The report of a previous case shows that glycosuria can be absent when this lesion is present, at least in the initial stage of the lesion. A patient previously mentioned (F. N. [no. 5]) was not found to have alimentary glycosuria of diabetic type until one and one-half months after the first examination, when the blood sugar increased to 0.245 per cent. In the present case, however, the blood sugar curve was perhaps not normal, as it showed an unusually slow fall toward the initial value. With the demonstration of a lesion in the pancreas, one may assume that this slow fall is due to a morbid condition of the pancreatic islands.

Finally, the roentgen-ray observations—that is, the shadows of calculi in the pancreas—confirmed the diagnosis.

Nontropical sprue is the only disease that might be considered in a differential diagnosis. The diagnosis of this condition was contra-indicated in the present case by (1) the pronounced steatorrhea with production of the oily mass; this symptom—to my knowledge—is not met with in sprue; (2) the slight saponification, as the soaps (determined as fatty acids) made up only 5.4 per cent of the excreted fats; (3) the marked azotorrhea in which the elimination of nitrogen was about three times larger than normally; (4) the disturbance of the internal secretion of the pancreas, and (5) the absence of stomatitis; (6) the mild anemia, which was not of a pernicious type; (7) and the absence of disturbances of the gastro-intestinal tract previous to the attacks of fatty diarrhea.

From the objective signs, the fatty diarrhea with azotorrhea and the somewhat abnormal blood sugar curve, one must conclude that a diffuse lesion of the pancreas was present, and that this lesion had attacked the islands of Langerhans as well as acini. I know of only two such diffuse lesions of the pancreas, diffuse carcinoma of the pancreas and chronic pancreatitis. Diffuse carcinoma of the pancreas is a rare condition, and the long duration of the illness excludes the possibility of that lesion in this instance. It therefore must be assumed that this case was one of chronic pancreatitis with extensive calculus formation, as evidenced by the roentgenograms. As far as I know, pancreatic calculi have been demonstrated in every case of more or less advanced chronic pancreatitis in which autopsy has been performed; of course, there has been a great deal of discussion as to whether this calculus formation is the primary process and the cause of the pancreatitis, or vice versa, but the question has not been settled conclusively. Hansen [9] recently reported a similar case in which autopsy was performed. Still, it is by no means a constant phenomenon that pancreatic calculi involve an abnormal excretion of fat, as is evident from a case reported by Jaquelin and Quénu.[10] In my case, however, it seems reasonable to assume that the calculi are contributory—and perhaps markedly so—to the severe impairment of the external function of the pancreas.

On the whole, the causes of chronic diffuse pancreatitis are not well known. As I have pointed out, syphilis is of considerable importance as a cause, then tuberculosis, arteriosclerosis, and, perhaps, formation of calculi; none of the first three possibilities can be taken into consideration in this instance.

For the sake of comparison, I shall mention another case which I reported in the paper previously quoted. The patient was an architect (V. T.), aged 57, who contracted syphilis thirty years previously. He had suffered from constipation since he was 26 or 28 years of age, and since the age of 38 had had colicky pains in the abdomen; these pains were diagnosed cholelithiasis. Fatty diarrhea was noticed one year ago, and glycosuria was noted at the same time. The patient was admitted to the Bispebjerg Hospital, where analysis of the metabolism (table 2) showed a daily loss of fat amounting to 132 Gm. and a loss of nitrogen amounting to 16.8 Gm. At the time of the patient's discharge from the hospital, the loss of fat was brought down to 21.3 Gm., and the loss of nitrogen to 3.23 Gm. At the same time, he was found to have diabetes with sugar in the urine amounting to as much as 6 per cent, diacetic acid, blood sugar (fasting) 0.296 per cent

9. Hansen, Svend: Ugesk. f. Laeger. **88**:328, 1926.

10. Jaquelin and Quénu: Arch de mal. de l'appar. digest. **17**:384, 1927.

and diuresis 3,000. He improved still more after being discharged, and the color of the feces became normal, but the glycosuria persisted. He died one year later from acute pneumonic tuberculosis. At this time, the stools were a normal color and contained but few droplets of fat (microscopic examination).

Comparison of this case with the preceding one shows two cases of chronic diffuse pancreatitis which, with regard to clinical symptoms, illustrate the extremes of changes in the fat, protein and carbohydrate metabolism which this disease involves. The last case of relatively quick recovery from fatty diarrhea in a diabetic patient is closely related to that form of diabetes which was called Hirschfeldt's [11] pancreatogenous diabetes, and in which the ability to digest fat—sometimes also protein—is lowered, at least periodically; the second case, then, is a case of diabetes in which the inflammation is not localized to the pancreatic

TABLE 3.—*Transition Types of Disease Between Two Extreme Types of Pancreatogenous Fatty Diarrhea*

Disease	Internal Secretion	External Secretion
Diabetes	Abnormal	Normal
Hirschfeldt's diabetes	Abnormal	Slightly abnormal
Pancreatogenous fatty diarrhea with azotorrhea and diabetes	Abnormal	Strongly abnormal
Pancreatogenous fatty diarrhea with azotorrhea and alimentary glycosuria of diabetic type	Slightly abnormal	Strongly abnormal
Pancreatogenous fatty diarrhea without azotorrhea, but with alimentary glycosuria of diabetic type	Slightly abnormal	Abnormal
Pancreatogenous fatty diarrhea with azotorrhea and abnormal blood sugar curve without glycosuria	Almost normal	Strongly abnormal
Pancreatogenous steatorrhea with or without azotorrhea, normal sugar metabolism, pancreatic calculi, cancer of caput pancreatis and Vater's papilla	Normal	Abnormal

islands but has extended to the glandular acini as well. The first case, on the other hand, with the marked impairment of the external pancreatic function and the slight damage to the pancreatic internal secretion, forms the transition to the rare cases of steatorrhea (usually not fatty diarrhea) which are due to localized lesions in the head of the pancreas or its surroundings (Vater's papilla). Such lesions cause a purely mechanical obstruction of the pancreatic duct; they usually do not show any sign of damage to the internal secretion. There are several transitions between these two extreme types of pancreatogenous fatty diarrhea, as shown in table 3.

I shall review briefly the disturbances in the digestion of fat, protein, and carbohydrates which chronic diffuse pancreatitis can give rise to, even though it does not always do so. The clinical experience on this point, on the whole, agrees well with the experimental investigations, and it has been demonstrated that this condition may be associated with

11. Hirschfeldt: Ztschr. f. klin. Med. **19**:294, 1891.

an impairment in the digestion of fat sometimes also of protein, while the digestion of carbohydrate (starch) is always normal (Müller,[12] Deucher,[13] Abelmann [14]).

With the experimental results in mind, one would expect chronic diffuse pancreatitis to be more advanced in cases of fatty diarrhea that are complicated with azotorrhea than in those cases in which the digestion of protein is normal. And if one takes an increased loss of fat as an indication of an aggravation of the pancreatic condition, as illustrated in table 4, one finds this to hold true. There is no azotorrhea associated with a relatively small loss of fat, and the azotorrhea is aggravated with the increasing loss of fat.

It is important that the digestion of carbohydrate is sustained to its full extent in pancreatogenous steatorrhea, because it is essential to cover the deficiency in the digestion of fat and protein by an abundant supply of carbohydrates. If the pancreatogenous fatty diarrhea is

TABLE 4.—*Relation Between Loss of Nitrogen and Fat in Six Cases of Pancreatogenous Fatty Diarrhea*

Name	Age	Sex	Daily Intake of of Fat, Gm.	Daily Excretion of of Fat, Gm.	Loss of Fat in per Cent	Daily Intake of Nitrogen, Gm.	Daily Excretion of Nitrogen, Gm.	Loss of Nitrogen per Cent
N. I.†	66	♂	95	13	13 #	15.6	1.65	11
V. H.	36	♂	98	29.9	30.5	16.2	2.6	16
C. J.	55	♂	95	56.9	60	15.6	4.3	27.6
J. N.	46	♂	108	88.4	81.8	18.9	8.9	47
V. K.*	43	♂	136	101	74.3	19.84	9.63	53.9
V. T.	57	♂	95	132.5	139.5	17.6	16.8	97

* Results of last examination.
† The case reports of patients N. I., V. H., C. T. and V. T. are published in a previous paper (Acta med. Scandinav. **64**: 292, 1926).
# The result is approximate.

complicated with diabetes, the dietetic treatment is complex, for one cannot give the patient large amounts of fats or proteins without aggravating the diarrhea. In most of these cases, however, the diabetes is rather mild and does not require any strict dietetic regimen. In one of my patients (V. K.) I found, as already mentioned, a lowered ability to digest starch, objective signs of fermentation dyspepsia, starch in the stools, granulose-containing bacteria and increased fermentation: on that account, I endeavored to ascertain how much the ability to digest starch was impaired. The amount of starch in the stools was determined four days in succession; it was found to be, respectively, 0.88, 0.32, 1.16 and 0.20 Gm. This loss must be said to be small, as the total intake of carbohydrates was 268 Gm. (J. Mayrhofer's method was used for the quantitative starch determination).

12. Von Müller, F.: Ztschr. f. klin. Med. **12**:45, 1887.
13. Deucher: Cor.-Bl. f. schweiz. Aerzte. **11**:321, 1898.
14. Abelmann: Inaugural Dissertation, Dorpat, 1890.

In the present case there is definite evidence that the pancreas is abnormal, namely, the presence of calculi. Hardly any one would dispute the right to assume that there is a relationship between the pancreatic lesion and the demonstrated disturbances in the digestion of fat and protein. The lowered ability to digest protein is readily understood when one assumes that the secretion of pancreatic trypsin or its hydrolytic power is lower than normally. But for the present I fail to understand the chief symptom of the condition, the fatty diarrhea; I cannot explain why these patients eliminate so much more fat than do normal persons.

In order to make this clear, it is well to review the process of normal digestion and absorption of fat as Pflüger [15] presented it in the beginning of this century; for his view still prevails.

As is well known, the main thought in Pflüger's theory is that the fat must be brought into a water-soluble form in order to be absorbed. The neutral fats of the food are hydrolyzed by the pancreatic lipase and other lipolytic enzymes of the intestinal content into free fatty acids and glycerin. The free fatty acids are dissolved by the bile, and they combine with the alkalis of the bile and the intestinal content (sodium carbonate according to Pflüger) into soaps, which are absorbed. Within the epithelial cells of the intestines, the soaps are converted into neutral fats, as the glycerin likewise is absorbed; either the alkalis are secreted back into the intestinal tract, or they enter the blood stream and are eliminated with bile and pancreatic and intestinal juice, whereafter they again are utilized for saponification. A normal absorption of fat depends largely on the emulsification of the fats, for emulsification makes the fats more susceptible to the action of lipase on account of the larger surface. This emulsification of the alimentary fats is principally accomplished by the bile and the soaps; the pancreatic juice is also said to emulsify fats.

An abnormal elimination of alimentary fats might well be thought to be due to one of the following three causes: (1) defective hydrolysis of the fat on account of an insufficient production or action of the lipolytic enzymes, particularly pancreatic lipase; (2) deficient saponification, and (3) defective emulsification of the fats. It is an obvious conclusion that the cause first mentioned might be the explanation of the steatorrhea in pancreatogenous fatty diarrhea, as the external and internal secretion of the pancreas has been found to be abnormal. But this explanation cannot be accepted as a matter of course, for the greatest number of cases of pancreatogenous fatty diarrhea show a normal or only slightly impaired hydrolysis of the alimentary neutral fats.

15. Pflüger: Arch. f. Physiol. **82**:354, 1900.

I think that the neutral fats in feces rarely amount to so much as was found in the patient in this case at the time of the last examination, the neutral fats being 57.8 per cent of the fecal fats. Gross [16] found as little as from 12.4 to 8.9 per cent, Salomon [17] 9 per cent, and Almagia 7.25 and 4.07 per cent neutral fats in the fecal fat content. Usually the figures are larger, however, varying from about 30 to 40 per cent, that is, hydrolysis is normal or only slightly impaired. Consequently, the cause of the fatty diarrhea cannot be a defective hydrolysis of the alimentary neutral fats, not in most instances at any rate. May it then be explained by assuming that soaps are formed in an abnormally small quantity? This view might appear to be sustained by two facts: In the first place, a large amount of free fatty acids is found in the feces (up to 89 per cent of the fecal fat content, Gross) in advanced cases of pancreatogenous fatty diarrhea; in the second place, the amount of soap in the feces in such cases is abnormally small. Still, a defective saponification can hardly be the cause, for one must assume that the bile, the intestinal juice and the pancreatic juice contain alkalis sufficient for the normal extent of this process. Nor is saponification a process which has to be accomplished all at once—no more so than the production of free fatty acids from the neutral fats. The process takes place gradually; as the new-formed soaps are absorbed, alkalis are set free for combination with the hydrolyzed acids.

The fact that the feces in pronounced cases of pancreatogenous fatty diarrhea contain only a small amount of soaps cannot be considered as supporting the view that saponification in the small intestine is abnormally poor; for the fecal soaps are the slightly soluble calcium and magnesium salts, while the soaps absorbed, according to Pflüger, are mainly the soluble sodium soaps. If there were any connection between saponification in the intestines and the fecal soap content, one would expect to find few soaps in acholic steatorrhea, and this is by no means the rule. Calcium and magnesium soaps in feces originate chiefly from the presence of these two metals in the food, and thus they do not have any bearing on the question of the absorption of fat.

As to the last possibility—that the fats or the fatty acids are not emulsified—it is not probable, as Pflüger has shown that the bile is able to make all the hydrolyzed fats water-soluble, and more besides. This explanation then would necessarily be contingent on an abnormality of the bile in pancreatogenous fatty diarrhea; but there is no plausible evidence that this is the case. It is known that in some cases of pancreatogenous fatty diarrhea the liver also can be the site of a chronic inflammation—and this coincidence is most frequent in syphilitic pan-

16. Gross and Guleke: Die Erkrankungen des Pancreas, Julius Springer, Berlin, 1924.

17. Salomon and Almagia: Wien klin. Wchnschr. **121**:870, 1908

creatitis—but in cases of pancreatogenous fatty diarrhea, autopsy usually shows a macroscopically normal liver.

In weighing the evidence from an analysis of the fecal fats, I cannot reasonably explain the fatty diarrhea by assuming a defective fat cleavage due to a lowered splitting up of the fats, nor by the supposition of a lowered formation of soaps or of a defective emulsification of the fats. The mere fact that some of the fecal fat in severe pancreatogenous fatty diarrhea is excreted as an oil-like mass, chiefly composed of neutral fat, is not proof of a defective emulsification of the fat in the small intestine. And as the increased peristalsis, which produces diarrhea, does not imply a substantial lowering of the absorption of fat, I thus cannot explain the cardinal symptom of the condition; namely, the fatty diarrhea.

Of course, attempts have been made to explain this peculiar condition, for it is only reasonable that the idea of the pancreatic lesion as the cause of the excretion of fat could not be dismissed. The view first presented is that the fat cleavage found in pancreatogenous fatty diarrhea is due to bacterial action and not—or only in part—to the pancreatic lipase; consequently, a large portion of the fat would pass down into the colon as neutral fat and would not be hydrolyzed until it reached this intestine. Concerning this it may be said that even though intestinal bacteria are capable of splitting neutral fat, this cleavage is rather insignificant, according to von Müller's investigations with adults and Escherich's [18] investigations with children. On mixing feces with neutral fat (milk), von Müller found that the cleavage varied a great deal at 37 degrees, the highest value being about 13.4 per cent of the neutral fat. Schiff, Kochmann [19] and Michaelis [20] have investigated various strains of the colon bacillus without being able to demonstrate any lipolytic ferment. It is possible, however, that the small amount of soaps in the feces in cases of pancreatogenous fatty diarrhea might be interpreted as being due to a cleavage of the calcium and magnesium soaps by intestinal bacteria (Alsleben [21]). That intestinal bacteria (bacteria in colon) bear some part in the fat cleavage is probable, as normal persons show a higher percentage of hydrolysis in the fat content of the rectum than in that of the small intestine. Thus Umber and Brugsch [22] found that 30.2 per cent of the fat content in a normal man was hydrolyzed in the duodenum, 68.9 per cent was hydrolyzed in the lowest part of the ileum and 81 per cent in the rectum. Ten per cent would then be the maximum of fat cleavage by the intestinal bacteria.

18. Escherich, quoted by von Müller.
19. Schiff and Kochmann: Jahrb. f. Kinderh. **49**:181, 1922.
20. Michaelis: Ztschr. f. Immunitätsforch. u. exper. Therap. **36**:449, 1923.
21. Alsleban, M.: Handb. d. norm. u. path. Phys. **3**:1035, 1927.
22. Umber and Brugsch: Arch. f. exper. Path. u. Pharmakol. **55**:164, **1916**.

and this figure agrees well with those of von Müller. Abelmann found similar proportions in dogs. In order to explain the considerable cleavage of fat in pancreatogenous fatty diarrhea—it may even amount to 95 per cent of the fecal fat content (Gross)—as largely due to bacteria, one must attribute to the intestinal bacteria such a strong lipolytic power as is contrary to all published results of investigations of this question.

Another theory tends to show that the pancreas has an internal secretion which acts on the absorptive faculty of the intestines. The theory was first advanced by Lombroso;[23] and he founded it on the following experimental observations:

If in dogs a pancreatic fistula is produced in such a manner that all the pancreatic juice escapes through the fistula, or if the head and the ducts of the pancreas are extirpated while some of corpus and the tail are left in place, or if the pancreas is extirpated and then implanted in the abdominal wall, these injuries will—according to Lombroso's experiments—lower the absorption of fat from 8.1 to 44.1 per cent after ligation of the pancreatic ducts, from 11.4 to 22 per cent with Pavlov's fistula and from 22.6 to 73.2 per cent after transplantation of the pancreas into the abdominal wall. If the pancreas is completely removed from the animals operated on in this manner, the loss of fat will exceed 100 per cent.

As Lombroso did not succeed in improving the absorption of fat in such animals by introducing liberal amounts of pancreatic juice into the duodenum, he concluded that the pancreas has an internal secretion which influences the absorptive faculty of the intestines. In a later paper, he further elaborates his theory by demonstrating that dogs on which pancreatectomy has been performed eliminate fat in excess of the intake with a melting point different from that of the fat ingested. Thus the pancreas would be able to transfer fat from the fat depots to the intestines.

Lombroso's experiments, however, have been criticized a great deal, first by Pflüger, who considers his determination of the absorption values to be incorrect, and who is unable to subscribe to Lombroso's denial of the presence within the gastro-intestinal tract of secretions which can fill the place of the pancreatic juice. Further, Burchardt[24] has not been able to confirm the results of Lombroso's experiments, but some observations by Hédon, Lüthje, Falta, Grote and Stähelin (references to the literature are given by these authors) on the increased waste of proteins and fats in pancreatectomized dogs support the view that the pancreas is of importance in the protein and fat metabolism—

23. Lombroso, Ugo: Arch. f. exper. Path. u. Pharmakol. **56**:357, 1907.

24. Burchardt: Arch. f. exper. Path. u. Pharmakol. **58**:251, 1908.

just as it most decidedly is so in the carbohydrate metabolism. Falta, Grote and Stähelin think that through internal secretion the pancreas secretes a substance which restricts the combustion of fat in normal persons and likewise, to some extent, the protein metabolism. In that respect it is worthy of mention that clinicians speak of a pancreatogenous adiposity. All these investigations, however, merely intimate that the function of the pancreas is more complex and covers more phases than those known so far, namely, its external function and its part in the carbohydrate metabolism; they do not explain why the fat cannot be absorbed in pancreatogenous fatty diarrhea.[25]

In view of the rather large discrepancies in the results of experiments on metabolism by various authors, after partial or total pancreatectomy (Abelmann, Vaugham Harley,[26] Lombroso, Burchardt, Fleckseder,[27] Hédon and Ville, McClure, Vincent and Pratt [28]), and considering that the same author using the same technic secures such different results with different dogs, one can only agree with Pratt in his conclusion that dogs vary a great deal in their ability to absorb fat after pancreatectomy. Even after total pancreatectomy some animals can absorb a large amount of fat, while others excrete all the ingested fat and more.

I shall briefly mention the anatomic observations in case V. T., the history of which has been given. The values obtained in the metabolism tests on this patient are given in table 2 (V. T.). As already mentioned, the fat and protein metabolism remained almost normal for about one year after the patient's discharge from the hospital, with formed feces of normal color and with few fat droplets in the feces on microscopic examination. The pancreas consisted of a lump of fibrous tissue, slightly larger than a hazelnut, corresponding to the head of the pancreas, and a coat of fibrous tissue from 2 to 3 mm. in thickness enveloping the dilated duct which contained a few calculi ranging in size from that of a pea to that of a millet seed.

Microscopic examination showed that the largest part of the organ consisted of connective tissue with some perivascular round cell infiltration, more marked in the cauda than in the caput, and numerous dilated

25. Hill and Bloor (J. Biol. Chem. **53**:171, 1922) have examined the fecal fat content after intake of meat and coconut-oil and have found its melting point to be constant, regardless of the food. According to their opinion, this indicates that fat is not secreted in the intestines, but that the ingested fat normally is completely absorbed, and that the fecal fat content is derived from intestinal juice, bile, leukocytes, etc.

26. Vaugham, Harly: J.Physiol. **18**:1, 1895.

27. Fleckseder: Arch. f. exper. Path. u. Pharmakol. **59**:407, 1908.

28. McClure, C. W.; Vincent, B., and Pratt, J. H.: J. Exper. Med. **25**:381, 1917.

secretory ducts. Of the glandular tissue, only a few remnants of acini remain in isolated spots and a few evidently hypertrophic islands. The specimen weighed 25 Gm. (the normal weight of the pancreas is from 100 to 120 Gm.).

It is astonishing, to say the least, that such an atrophic pancreas from which the acinar gland tissue has almost completely disappeared should be able to maintain an almost normal absorption of fat. But the case is not exceptional. Von Müller reports a case of almost complete atrophy of the pancreas in which the digestion of fat was normal and the digestion of protein only slightly impaired; he cites this case as evidence of his view that the pancreas is not of great importance in the digestion of fat. In 1925, Labbé [29] had a similar case in which the digestion of fat and protein was normal. At no time during their sickness did either of these two patients have fatty diarrhea.

I cannot get away from the fact that atrophy of the pancreas—just like pancreatectomy in animals—is tolerated differently by different persons, even though this condition usually implies considerable disturbances in the digestion of fat and protein. Consequently, some persons are more capable than others of mobilizing their auxiliary digestive ferments and of accomplishing the absorption of their cleavage products. But the process is not known. It is probable that chronic diffuse pancreatitis with its slow progress gives the organism a better chance of attaining this end than does experimental pancreatectomy. It is not surprising that an extensive formation of calculi in the pancreas, as in the case reported here with large concrements in the caput—most likely in Wirsung's duct—is more apt to cause a severe and protracted impairment of the digestion of fat and protein than is the insidious chronic pancreatitis, with less extensive stone formation. In the six cases of pancreatogenous fatty diarrhea that I examined previous to this case, the fatty diarrhea was transitory and of short duration (from two months to about one year), and it yielded to suitable treatment. In this case it was aggravated.

Cases of fatty diarrhea in connection with chronic diffuse pancreatitis, or rarely with a diffuse carcinoma of pancreas—are encountered, but I am unable to explain the origin of its chief characteristic, the abnormal elimination of fat. Cases of chronic diffuse pancreatitis in which the glandular structures are almost completely destroyed are seen, and I fail to understand why these cases are not associated with fatty diarrhea; and yet there is no doubt that the pancreas is important to the assimilation of fat in the intestines. Finally, one encounters fatty diarrhea in cases in which neither the pancreas, the intestines nor the bile

29. Labbé: Arch. de mal. de l'appar. digest. **14**:581, 1925.

appears to be abnormal, namely sprue. I therefore cannot explain the pathogenesis of fatty diarrhea.

Treatment.—The metabolism tests showed that it was necessary to restrict the intake of fats and proteins as far as feasible, as a more plentiful supply of these substances merely would increase the diarrhea. The patient gained 22 pounds (9¾ Kg.) by increasing his intake of carbohydrates—plenty of bread (he ate as much as thirty slices of bread a day!) porridges, fruits, vegetables, honey, marmalade and beer—a diet poor in fats and relatively poor in proteins. He again became normal as to body fat. He was given five tablets of 0.5 Gm. of a preparation containing pancreatin with 10 per cent of tannin a day for a period of five days, during which time the daily amount of feces was 670 Gm.; in the five days preceding this period the amount was 570 Gm. a day; and in the five days following the discontinuance of pankreon, the administration of the amount was 670 Gm. a day. Pankreon thus did not have any effect on the amount of feces which are composed mostly of fat and undigested or partly digested proteins. Throughout the entire period, the stools were of formed consistency, usually two stools a day. The diet mentioned had the effect that the stools gradually looked more natural. But, as shown on examination, this improvement did not signify that the patient really did digest the fat better than before; it was merely due to the decrease of fats in the diet. On the whole, the total daily amount of feces had decreased; during the first fifteen days on this diet, the stools on an average amounted to 650 Gm. a day, during the last fifteen days to 525 Gm. The interval between these two periods was about six weeks.

SUMMARY

Description is given of a case of pancreatogenous fatty diarrhea, caused by a pancreatitis of unknown etiology that was complicated with extensive calculus formation in the secretory ducts.

This case presents two of the cardinal symptoms of pancreatogenous fatty diarrhea, namely steatorrhea and azotorrhea, the third cardinal symptom, permanent or alimentary glycosuria of diabetic type was absent.

The pathogenesis of the fatty diarrhea is discussed on basis of Pflüger's theory.

A case of almost complete atrophy of the pancreas with normal or only slightly lowered fat absorption is mentioned.

The possibility that pancreas contains a substance which influences the absorbtion power of the intestine by way of the blood, is discussed.

PEPTONE TREATMENT IN BRONCHIAL ASTHMA*

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Although the statement may seem somewhat sweeping, it is nevertheless a fact that a study of bronchial asthma has not yet been presented which might reasonably be viewed as conclusive. This must of necessity be true, because the asthmatic state has become so inextricably involved, not only with the question of anaphylaxis, but likewise with theories of desensitization. And since it is recognized that there is still lacking a thorough understanding of the phenomena of shock and sensitization—on which both anaphylaxis and desensitization have a bearing—the ultimate solution must still be sought.

The conviction that immunization to be effective must be carried out by specific means—largely the work of von Behring and Ehrlich—was somewhat shaken more than thirty years ago. It was then that the theory of nonspecific desensitization was first inaugurated.

This was accomplished through the work of Buchner, Römer, Kühne, Rumpf, Matthes, Bauer and numerous others, who, by both experimental and clinical demonstration with a number of dissimilar substances, seemed to establish the validity of their theory.

As early as 1895, Matthes,[1] in the therapy of tuberculosis, obtained a reaction following the administration of deuterproteose which was similar to, or identical with, the reaction previously considered specific for tuberculin.

Among other pioneers, the name of Rumpf [2] stands out prominently. On the basis of experimental work done by Buchner, Rumpf treated with subcutaneous injections of a pyocyaneus vaccine a series of patients who had typhoid fever, achieving results as promising as those obtained by Fränkel with typhoid vaccine. It was Rumpf who, at this early period, called attention to the phenomenon now termed anaphylactic shock, consisting of chills, sweating and a fall of temperature and pulse rate following these injections. He also noted that the earlier this therapy was administered in the course of the disease, the better the results, and called attention to the state of well-being experienced after the injection.

Again, Ichikawa,[3] working independently, reported in 1912, and again in 1914 results just as satisfactory in paratyphoid fever with intravenous injections of typhoid vaccine as he had obtained in typhoid.

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* From the Department of Applied Immunology of the French Hospital and Fifth Avenue Hospital.

1. Matthes, Max: Deutsches Arch. f. klin. Med. **54**:39, 1895.
2. Rumpf, T.: Deutsche med. Wchnschr. **19**:987, 1893.
3. Ichikawa, S.: Ztschr. f. Immunitätsforsch. **23**:32, 1914-1915.

About the same time, Kraus,[4] having investigated the splendid work which had been accomplished in the treatment of typhoid with the intravenous use of colon vaccine, applied the same therapy in puerperal infection, septicemia, scarlet fever and plague, obtaining similarly successful results.

On these and on additional observations and results, the modern conception of nonspecific therapy has gradually been built. It had been shown that astounding physiologic effects could be produced in human beings as well as experimentally with various nonspecific antigens.

Various proteins and protein derivatives have been employed. In 1910, Schmidt had injected milk intramuscularly; Lüdke introduced the injection of proteoses or albumoses, and Mittländer employed hypertonic salt solution. Distilled water, small doses of turpentine, coloidal metals, nucleic acid, lipoids, enzymes and numerous other substances capable of producing a general reaction—today known as shock, anaphylactic reaction and allergy—were administered.

As a result of these observations and of increased clinical results, a mass of literature has accumulated, setting forth varying views on every phase of this vast question—the phenomenon of the reaction, immunization and anaphylaxis, the efficacy of nonspecific therapy in general and of the proteins in particular (including substances such as milk, gelatin, globulin, enzymes, normal serum, peptone and egg white), the question of dosage, the advantage of various means of administration and numerous other phases.

In nonspecific therapy, as in every newer mode of therapy, the success which attended it may have led to overenthusiasm in its employment. It must not be forgotten, however, as Zinsser [5] has pointed out in his book that the entire problem is still clothed in considerable mystery and is entirely too complex to be dealt with even in a book of that scope.

The fact that varying degrees of success have been attained with a particular form of protein in persons suffering from an apparently identical disorder, or in the same subject at different times, has led therefore to much consideration by various investigators. And it is perhaps through an analysis of their deductions that a solution of the problem may eventually lie.

Petersen [6] states that "protein therapy offers a possibility, perhaps the most powerful at our command, for the alteration of the current of cellular activity, either in the direction of acceleration of function or

4. Kraus, cited by Petersen (footnote 6).

5. Zinsser, Hans: Infection and Resistance, New York, Macmillan Company, 1923.

6. Petersen, W. F.: Protein Therapy and Non-Specific Resistance, New York, Macmillan Company, 1923.

depression of function," but he admits that its application should be limited to certain stages of the disease process. In this connection, he states:

> If nonspecific therapy is after all merely a method that deals with heretofore known reactions, we must be prepared to accept the probability that it obeys all the commonly observed laws of biologic reactions. If we regard it as a method of stimulation—plasma activation—it follows that it can only be effective when the protoplasm is still in fit condition to respond to stimulation. Once the stage of exhaustion has been reached, the mere irritation of the nonspecific agent is no longer able to bring about any alteration in the disease process other than aggravation.

Many believe, with Petersen, that the patient does not become sensitized to the proteose injections, but that in this way a degree of tolerance is established in which subsequent injections do not give an equal response. Likewise, Novy, de Kruif and Novy [7] are of the opinion that peptone itself is not toxic, but when brought into contact with a reactive serum or plasma it brings about the change which results in anaphylatoxin production.

Karsner and Ecker,[8] in a study of the desensitized state in serum anaphylaxis, tell that "nonspecific, usually transitory reduction of shock, has been produced by an injection of various substances, but the final issue as regards specificity of this phenomenon is still a matter of considerable dispute." These investigators quote Thomson,[9] who believes that much depends on the degree of sensitiveness in each subject as well as on the particular time of desensitization. They also cite Massini [10] who, following much experimental work, concludes that anaphylaxis is specific, but that, in addition, there is present a nonspecific element. This latter theory is also sponsored by Schiff [11] and others.

The theories referred to will no doubt suffice to indicate the general lack of agreement on the subject under consideration in the present article.

VARIETY OF PEPTONE

In regard to the variety of peptone employed in the treatment of patients with asthma, it seems logical to expect that the chemical composition of the particular brand administered would exert a definite characteristic influence. Such, however, does not seem to be the case, as will be noted from the following reports gathered from the literature.

Novy, de Kruif and Novy,[7] using Witte's peptone, found it less toxic than agar when employed experimentally. In 1927, Auld [12] reports

7. Novy, I. G.; de Kruif, P. H., and Novy, F. O.: J. Infect. Dis. **20**:657, 1917.
8. Karsner, H. T., and Ecker, E. E.: J. Infect. Dis. **30**:333, 1922.
9. Thomson: Ztschr. f. Immunitätsforsch. u. exper. Therap. **26**:213, 1917.
10. Massini: Ztschr. f. Immunitätsforsch. u. exper. Therap. **27**:194, 1918.
11. Schiff, Nathan: Am. J. M. Sc. **5**:664, 1918.
12. Auld, A. G.: Brit. M. J. **1**:829 (May 7) 1927.

unfavorably on results obtained when this brand of peptone was used exclusively, for the reason that it contains histamine. He found several other peptones "dangerous," and others "feeble, as they contain little proteose."

In 1923, Larsen, Haigh, Alexander and Paddock,[13] on the basis of the success previously (1920 and 1921) reported by Auld in the treatment of bronchial asthma with intravenous and intramuscular injections of a mixture of Witte's and Armour's peptone suspended in 0.85 per cent solution of sodium chloride employed Auld's method in a study on experimental animals. This therapy, as reported by these writers, not only yielded poor response but led them to conclude that "clinically the use of peptone intravenously, in bronchial asthma, according to the method of Auld, has been disappointing, and is considered dangerous."

Among numerous other workers, Miller and Raulston,[14] in 1923, and Ball,[15] in 1927, reported results obtained with intravenous injections of a 5 per cent solution of Armour's peptone in the treatment of patients with migraine. These writers believe that migraine, epilepsy, asthma, hay-fever, urticaria and angioneurotic edema are kindred disorders, all being evidences of anaphylaxis; among other observations they report the presence of eosinophilia in each of the conditions mentioned. Miller and Raulston state, furthermore, "that relief from peptone was temporary as in hay-fever and asthma." In Ball's cases, 15 per cent of the patients showed improvement, 35 per cent were markedly improved and 50 per cent were failures. Miller and Raulston's results approximated Ball's, with 16 per cent improved, 36 per cent markedly improved, and failures in 48 per cent of cases. Miller and Raulston, however, also quote Auld[16] who pointed out the special advantage of Armour's 5 per cent preparation over Witte's, the former containing a smaller amount of primary proteoses. Again, Miller and Raulston suggest that its action as a desensitizer may be due to the proteoses and not to the peptone itself, pointing to the fact that Auld could not secure favorable effects in asthma when pure peptone was administered. Peptone had a definite action in temporarily relieving migraine attacks in their experience, but noting the observations of other workers who reported marked urticaria following single injections, they ventured to suggest that "different preparations of the same brand no doubt differ in their composition."

Whether or not this last feature is an important phase of the subject, contributing to the unreliability of results, or whether still more momen-

13. Larsen, Haigh, Alexander and Paddock: J. Immunol. **8**:409 (Sept.) 1923.

14. Miller, J. L., and Raulstone, B. O.: Treatment of Migraine with Peptone, J. A. M. A. **80**:1894 (June 30) 1923.

15. Ball, F. E.: Am. J. M. Sc. **173**:781 (June) 1927.

16. Auld, A. G.: Brit. M. J. **1**:696 (May 14) 1921.

tous factors intervene, remains an open question. Much discussion has also centered about the questions of dosage and the mode of administration.

DOSAGE AND MODE OF ADMINISTRATION

Petersen [6] states:

> With nonspecific therapy, as with other new therapeutic procedures, there is still some uncertainty as to the proper dosage. Especially is this true because the dosage depends to some extent on the vigor of the patients, on the type of infection which is causing the disease, as well as on the stage of the disease.
>
> On the basis of the fact that in antianaphylaxis or desensitization a nonspecific element is at times observed, other methods have been devised which are sometimes applied more easily than the specific method that Walker has used. Only larger clinical experience will enable us to draw conclusion. It must be borne in mind, too, that our conception of protein therapy must not be limited to the intravenous injection of typhoid vaccine or peptone. Many of the milder reactions continued over a longer period of time may be found much more effective.

Auld reports on the use of injections of peptone (dissolved in physiologic solution of sodium chloride to which a small amount of sodium carbonate is added) given either intravenously or subcutaneously. Pagniez and Widal, Abrami and Brissaud use peptone by mouth, and Cordier uses enemas of peptone. Some require the continuous use of the peptone; others do better when it is given for from three to eight days followed by an interval of the same length.

On the whole, the administration of peptone has been accomplished by different routes, each method in turn being advocated or discarded by the various investigators. Pasteur Vallery-Radot and Blamoutier [17] following a three years' experience with peptone, believe that intradermal injections are beneficial in cases of hay-fever and essential asthma in which the attacks are frequent. They advise that this treatment be administered during the attack. Patients with spasmodic coryza improved, although relief was of short duration. These writers administered either Witte's or Chassing's peptone. (The technic and dosage will be described toward the end of this article.) The entire series consisted of twenty injections, administered once a day. Care was exercised to inject the solution into the skin; injected beneath the skin, a phlyctena and sloughing may ensue, according to these observers.

In connection with subcutaneous injections of peptone, Schiff [11] reports splendid results clinically with a 33.33 per cent solution of Armour's dry peptone. Three minims (0.18 cc.) of this solution he believes to be a safe dose. This was increased by 1 minim (0.06 cc.), up to 1 cc., at biweekly or triweekly intervals. Schiff, guided by experience, gages the dosage according to the symptoms and progress of the

17. Vallery-Radot, Pasteur, and Blamoutier: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:491 (May 5) 1927.

individual case. In the event of a severe local reaction, he repeats the preceding dose. Early recognition of the approach to the limit of tolerance is regarded as of great importance.

Walker,[18] however, reports that benefit was not derived in a few nonsensitive asthmatic patients, from large doses of peptone, also administered subcutaneously. Walker states in this connection:

> This method of treatment is dangerous unless the patient is tested with peptone to rule out the possibility of his being sensitive to it. We feel that this fad of injecting patients with proteins to which they are not already sensitive is, in general, apt to be a mistake.

Larsen, Haig, Alexander and Paddock[13] administered peptone (Chapotaut's peptone tablets) by mouth in a few cases of bronchial asthma, but with negative results. It was equally disappointing in patients with urticaria, who were given these tablets in doses of from 0.1 to 0.3 Gm. fifteen minutes before meals.

In their search for a satisfactory method, Larsen, Haig, Alexander and Paddock thereupon employed the technic used by Auld in this earlier work (20: 16) which consisted of administering intravenously a 5 per cent suspension in 85 per cent solution of sodium chloride, of a mixture of Armour's and Witte's peptones, in ratio of 3: 1. Here again, they report that "clinically the use of peptone intravenously in bronchial asthma, according to the method of Auld,[19] has been disappointing and is considered dangerous."

Novy, de Kruif and Novy,[7] in an experimental study in which Witte's peptone was injected intravenously, found that the symptoms and conditions of guinea-pigs and white rats so treated were identical with those produced by anaphylatoxin, by agar, or by specific anaphylactic shock. The average lethal dose for guinea-pigs they report as 0.3 Gm. per kilogram, that for the rat being 2 Gm. per kilogram—an amount seven times larger than for guinea-pigs. In rabbits, in addition to the usual symptoms, such as dyspnea, spasms and convulsions, a striking exophthalmos was noted, also a great drop in blood pressure and a marked decrease in coagulation time. The rabbit was found more resistant than the rat, the least amount of peptone which was fatal being 3 Gm. per kilogram. These animals showed an immunity or tolerance to repeated injections of peptone, the same as shown on dogs and guinea-pigs.

These investigators, making additional experimental studies, tested the effect of injecting the anima's own serum treated with peptone and found that here also anaphylatoxin is produced. The transfusion of the

18. Walker, cited by Petersen (footnote 6).

19. Auld, A. G.: Brit. M. J. **1**:576, 1920.

blood of rats injected with peptone demonstrated that anaphylatoxin was formed in vivo.

In 1927, Auld, finding that the effect of peptone in human beings varies greatly, decided on the combined use of peptone, serum and agar in those cases which did not yield to peptone alone. He stated that while these substances "act in an entirely different manner, yet they bring about in animals the same result." Five cases are cited illustrating the splendid effects of this means of therapy in subjects previously treated with little or no success, either with peptone exclusively or with other treatment. Auld, however, admits that a few of his patients—a small percentage—did not respond to this newer therapy.

REPORT OF CASES

Based on the observations cited, I have employed various preparations of peptone, administered in accordance with numerous methods suggested. The entire series comprises sixty cases, grouped according to the following plan:

GROUP 1.—Intramuscular injections of a 5 per cent peptone (Armour's) solution, twice a week, for two months.

GROUP 2.—Intramuscular injections of a 5 per cent peptone (Armour's) solution, every day, for two weeks; then once a week, for two months.

GROUP 3.—Intradermal injections of a 30 per cent peptone prepared according to the method suggested by Dr. Pasteur Vallery-Radot and Blamoutier.[17]

Fifty grams of peptone are mixed with an amount of distilled water sufficient to make up 100 cc.; this is then stirred with a glass rod. It is left at room temperature or put in a water bath, stirring from time to time, and adding water to keep the quantity at 100 cc. for from twenty-four to forty-eight hours. It is then filtered through ordinary filter paper, this procedure taking several hours. The solution is put in ampules and sterilized. One cubic centimeter of this solution contains 0.5 grains of peptone.

The first injection consisted of 0.1 cc. of the solution; the second, 0.2 cc.; the following, 0.3 cc. The last dose was never exceeded. The entire series consisted of twenty injections, one administered each day.

GROUP 4.—Peptone powders by mouth in 5 and 10 grain (0.32 and 0.65 Gm.) doses, three times a day, one hour before meals, for two months.

GROUP 5.—Intravenous injections of 1 cc. of 5 per cent peptone solution, twice a week, for four weeks.

GROUP 6.—Intravenous injections of 2 cc. 5 per cent peptone solution, once a week, for four weeks.

GROUP 7.—Intravenous injections of peptone serum, according to the technic suggested by Auld, once a week, for four weeks (on five patients), and once a week for eight weeks (on five patients).

The results in the foregoing cases are as follows:

In groups 1, 2 and 3, ten cases each, benefits did not result. In group 4, there were also ten cases, in which benefits were not noted.

In group 5, five cases, slight temporary improvement was observed, but not sufficient to justify treatment. In group 6, five cases, there was slight improvement following each injection. In group 7, in which injections were given five patients for four weeks and five patients for eight weeks, respectively, benefits were not noted.

As will be seen from this study, the employment of peptone in the treatment of patients with bronchial asthma has been wholly disappointing in my series of cases. In evaluating this means of therapy, I heartily endorse the summarization of Dr. William S. Thomas [20] in a recent publication comprising a study of asthma, in which he says:

> Careful trial of various nonspecific protein methods of treatment of asthma has left me unconvinced of their value. It is difficult to explain the fact that peptone, for example, as a desensitizing agent and remedy for asthma is approved by English, French and some American writers, while almost all colleagues of my acquaintance, and I with them, have failed to obtain beneficial results from its use, either by the employment of methods of injection or by mouth administration.

SUMMARY AND CONCLUSIONS

After a careful and absolutely unbiased analysis of patients treated with peptone, I feel justified in stating that in my experience peptone is of no value in cases of bronchial asthma.

I hesitate to state this conclusion, in lieu of the favorable result published by such excellent observers as Pasteur Vallery-Radot, Blamoutier, Auld, Schiff and others.

47 West Fifty-Fourth Street.

20. Thomas, W. S.: Asthma, New York, Paul B. Hoeber, 1928.

CHEMICAL ANALYSES OF BLOOD IN PATIENTS HAVING SENILE CATARACT *

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A study of the chemistry of the blood in patients suffering from senile cataract was undertaken because we felt that since this type of cataract is always bilateral, it must be due to systemic changes. It was thought that changes in the blood might possibly point out lines of study which would eventually lead to a discovery of the etiology of these senile changes so frequently seen in the crystalline lens.

As far back as 1881, Cahn,[1] in Hoppe-Seyler's laboratory, following some earlier observations of Jacobsen, reported data on the composition of cataractous lenses, in comparison with those of normal eyes. In lenses exhibiting cataractous changes the figures show a marked increase in all lipids: cholesterol, lecithin and fats. The increase in cholesterol is particularly striking, being 0.62 per cent per hundred parts of the solid residue in normal lenses and 6.22 per cent in cataractous lenses.

In the series of cases studied, the analyses included cholesterol, urea nitrogen, sugar and hemoglobin; a number of other determinations were also made which are not recorded here, namely on uric acid, chlorides, calcium, inorganic phosphates, carbon dioxide content and the p_H, all of which were found to be essentially normal.

Since hypercholesterolemia is encountered in diabetes and in certain forms of nephritis, the figures for blood sugar and urea nitrogen are recorded as bearing on these possible complications.

Cholesterol was estimated by the Myers-Wardell method, blood sugar according to Folin-Wu, urea nitrogen by a nesslerization technic and hemoglobin by employing a Newcomer disk—all as described by Myers' text.[2]

Strictly normal figures for the cholesterol content of human whole blood may be given as varying from 140 to 170 mg. per hundred cubic centimeters. It will be noted that twenty-nine, or 54 per cent, of the

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1. Cahn, A.: Zur physiologischen und pathologischen Chemie des Auges, Ztschr. f. physiol. Chem. **5**:213, 1881.

2. Myers, V. C.: Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924.

fifty-four cases in our series show figures for cholesterol above 170 mg. Nine of the cases have figures for urea nitrogen varying from 20 to 23 mg., while three cases show blood sugars above 150 mg. There does not appear to be any direct relationship, however, between the level of

Blood Analyses in Patients with Senile Cataract

	Case	Age	Sex*	Date	Hemoglobin Gm.	Nitrogen mg. to 100 Cc. Urea	Sugar	Cholesterol	Remarks
1	A. B.	65	♀	2/ 9/27	14.7	12.9	107	519	Old trachoma
2	W. W.	82	♂	5/17/27	15.3	15.5	99	311	
3	J. C.	65	♀	7/ 1/27	13.2	11.5	91	264	
4	J. H.	65	♂	2/24/27	16.5	17.3	87	242	Mild diabetes
5	N. F.	69	♀	7/15/27	10.8	11.5	90	238	
6	J. Mc.	57	♀	12/ 7/26	12.4	15.8	113	224	
7	J. M.	47	♂	11/11/26	14.6	19.9	99	224	
8	M. C.	80	♀	3/31/27	15.3	12.2	139	218	Diabetic
9	M. H.	67	♀	6/10/27	12.7	14.4	105	206	
10	A. L.	65	♀	3/ 2/27	14.3	13.1	308	204	Diabetic
11	G. M.	72	♂	12/ 9/26	16.5	21.9	105	200	
12	L. R.	82	♀	7/13/27	15.2	19.5	115	200	
13	H. A.	84	♂	10/28/26	....	15.3	104	200	Stone in kidney
14	L. S.	74	♂	5/20/27	13.5	14.9	92	193	
15	F. B.	72	♂	6/30/27	15.2	21.8	84	190	
16	A. F.	71	♀	9/30/26	....	22.9	121	190	
17	W. W.	61	♂	7/20/27	12.8	13.8	105	188	
18	M. K.	..	♀	6/ 7/27	13.2	17.1	131	184	
19	J. R.	53	♂	12/11/26	14.5	18.5	85	183	Arteriosclerosis
20	D. L.	57	♂	6/30/27	15.2	22.2	89	182	
21	G. S.	58	♂	1/17/27	13.2	17.7	96	180	
22	L. M.	59	♀	6/ 8/27	15.2	13.3	107	179	
23	N. S.	52	♀	1/28/26	12.9	....	94	179	
24	G. M.	42	♀	6/15/27	15.1	10.1	100	178	
25	A. C.	67	♀	1/27/27	12.7	7.6	100	177	Adenomatous goiter
26	D. D.	..	♂	11/ 3/26	13.2	8.3	116	177	
27	F. L.	76	♂	1/ 4/27	....	14.7	111	174	
28	F. J.	17	♂	10/ 6/26	14.1	15.2	84	174	Complicated cataract
29	C. C.	58	♂	3/31/27	12.9	16.9	103	172	
30	M. M.	74	♀	10/ 5/26	13.4	13.5	98	170	
31	D. C.	62	♀	10/15/26	12.3	14.5	99	167	
32	P. B.	75	♀	11/ 3/25	12.3	15.9	99	167	Arteriosclerosis
33	M. M.	57	♂	11/30/26	15.2	11.9	105	167	
34	T. E.	79	♂	11/ 3/26	13.5	21.6	177	163	
35	H. M.	46	♂	10/ 8/26	14.2	16.6	88	163	
36	A. H.	68	♀	1/25/27	13.3	10.3	100	161	
37	P. R.	..	♀	3/ 9 27	17.3	12.4	107	160	
38	W. W.	72	♂	1/ 8/27	13.8	19.0	....	159	
39	M. Mc.	66	♀	1/28/27	12.7	17.0	82	158	
40	S. T.	72	♀	10/ 4/26	13.6	10.6	101	157	
41	J. S.	65	♂	12/10/26	14.4	22.2	153	156	Diabetic
42	H. K.	82	♂	4/15/27	11.5	18.0	139	154	Goiter (colloid)
43	B. L.	51	♀	2/23/27	12.7	12.7	90	154	
44	L. O'B.	65	♀	5/ 9/27	16.9	13.6	181	152	Diabetic
45	M. C.	70	♀	10/22/27	11.7	11.6	90	151	
46	H. L.	43	♂	4/13/27	14.1	14.0	101	148	
47	R. R.	76	♂	10/ 5/26	14.1	15.5	99	147	
48	L. U.	65	♀	4/ 6/27	12.1	11.0	98	144	
49	M. P.	..	♀	3/ 9/27	12.3	19.8	109	140	
50	J. C.	50	♀	5/11/27	13.5	9.5	98	132	Old chorioretinitis
51	A. N.	70	♂	5/ 4/27	16.0	15.4	93	130	
52	G. J.	88	♂	1/20/26	....	19.1	105	128	Arteriosclerosis
53	A. B.	80	♂	1/21/27	14.2	13.1	92	127	
54	W. J.	52	♂	12/12/26	13.9	15.2	105	121	

*In this column, ♂ indicates male; ♀, female.

the blood urea or sugar and the cholesterol, and it does not seem that the hypercholesterolemia may be ascribed to a renal or diabetic factor.

The observations on the blood cholesterol in patients with senile cataract are somewhat analogous to those in cholelithiasis, where efforts to show a direct relationship between hypercholesterolemia and choleli-

thiasis [3] have been disappointing in that, at the time of operation, a fairly large percentage of patients show perfectly normal figures for cholesterol, while in many others the hypercholesterolemia observed is due to jaundice. The presence of hypercholesterolemia at the time of the formation of gallstones, however, has never been disproved.

We believe that the rise in the cholesterol content of the blood observed in our series of cases is interesting, but we do not wish to place undue emphasis on it at the present time, although it may well be an important etiologic factor. One of us is now engaged in a study of the blood in noncataract cases in patients of similar age, and is extending the blood studies to cover the fat and lecithin; a study of the tolerance for sugar in patients having senile cataract is also being made. A study of the chemical make-up of cataractous lenses as compared with normal ones is also being undertaken.

Several analyses of lenses, made by Mr. P. W. Salit at our suggestion, are of interest. A normal lens showed 0.4 per cent cholesterol, whereas two cataractous lenses gave figures of 0.51 and 0.7 per cent with blood cholesterols of 0.166 and 0.205 per cent, respectively.

CONCLUSIONS

Chemical blood analyses have been made on a series of fifty-four cases of cataract. The observations on the blood were essentially normal except for the cholesterol, which was somewhat increased in 54 per cent of the cases. This observation is being further investigated.

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3. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, Arch. Int. Med. **20**:599 (Oct.) 1917.

PRESENILE DISTURBANCES OF BLOOD PRESSURE *

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Clinical experiences give evidence that about the end of the fourth decade of human life, and sometimes earlier, a period begins which may be regarded as presenile age,[1] and it is characterized by disturbances of the circulatory system besides many other alterations. The clinical symptoms of these disturbances are as follows: The blood pressure becomes higher on a constant level, and at the same time one finds various signs of cardiac incompetence, especially during physical work, such as increase in the pulse rate, precordial uneasiness and, sometimes, dizziness. The accommodative power of the blood pressure becomes unsteady, as demonstrated by its irregular fluctuation. Therefore, an investigation into the complicated mechanism of the origin of high blood pressure in persons of presenile age is justified. The problem is important, since it is connected with many interesting questions of disease in human beings.

The consideration of these questions may also bring out some practical points relating to the problems of hygiene, prophylactic medicine, life insurance, etc.

CRITICAL REVIEW OF METHODS FOR DETERMINATION OF BLOOD PRESSURE

Careful determinations of the blood pressure reveal many important data relating to the function of organs which regulate the blood pressure level. Functional changes in this system are often expressed by variation in the blood pressure level, as demonstrated by the investigations of Fahrenkamp,[2] who found interesting alterations by repeated measurements made during a day, and especially by measurements made early in the morning. C. Müller [3] and Katsch and Pansdorf [4] observed a striking diminution in the blood pressure of normal persons during

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1. This age corresponds to presenile age in my country and, I believe, in all Europe. Possibly it begins somewhat below or above this age in other parts of the world.

2. Fahrenkamp, K.: Ueber Hypertension, Ergebn. d. ges. Med. **5**:144, 1925.

3. Müller, C.: Die Messung des Blutdruckes am Schlafenden, Acta med. Scandinav. **55**:381, 1921.

4. Katsch, G., and Pansdorf, H.: Die Schlafbewegung des Blutdruckes, München. med. Wchnschr. **69**:1715, 1922.

sleep. All these observations, however, do not give one sufficient knowledge of the accommodative power of the system which regulates the blood pressure level—the vasomotor center, vasomotor nerves, etc.—but prove only the temporary differences in pressure. Therefore, one must look for functional tests.

By means of functional tests one can determine how certain organs or groups of them react to a certain amount of work, which is the function of the respective organs. Pharmacologic tests have been employed as a functional method in determinations of blood pressure, but the drugs used—epinephrine hydrochloride, caffeine, etc.—act on the involuntary nervous system, and are not a reliable means for judging the function of organs, since the involuntary nervous system often responds with a twofold reaction (Baráth[5]). More reliable functional methods, therefore, must be obtained. I have found that my "labor test" and "pscychic test," as established in previous papers,[6] are reliable for this purpose.

LABOR TEST OF BLOOD PRESSURE

It is well known that physical work is accompanied by a slight elevation of the blood pressure, which is of short duration, and often gives place to a slight decrease of the blood pressure. The elevation of the blood pressure and its duration can provide useful information regarding the state of the circulatory system, as shown by the investigations of Schrumpf.[7] In cases of circulatory incompetence, he found that elevation of the blood pressure, associated with an increase in the pulse rate, occurs for a long period of time. I observed later, in several patients, in whom there were no signs of circulatory insufficiency, a longer duration of the elevation of blood pressure after work without a persistent tachycardia. The explanation of this observation may be that in these cases the regulating mechanism of the blood pressure system is diminished: in other words, the regulating system has lost the power of compensating the hypertension caused by labor within a definite period. Apparently, the hypertension due to labor remains at a higher level much longer than it does under normal conditions.

In considering these preliminary experiments, I found the basis of the labor test, which is carried out as follows: The blood pressure of the patient is measured in the early morning hours, before breakfast, in a period of absolute rest. Then he is allowed to walk up two flights

5. Baráth, E.: On the Amphotropic Effects of Drugs upon the Vegetative Nervous System, Am. J. M. Sc. **172**:107 (July) 1926.

6. Baráth, E.: Arterial Hypertension and Physical Work, Arch. Int. Med., to be published.

7. Schrumpf, P.: Klinische Herzdiagnostik, Berlin, Julius Springer, 1919.

of stairs at a slow pace—in from two to three minutes. The blood pressure is measured immediately after his walk upstairs and then every half minute for from ten to fifteen minutes. The data obtained are registered in a curve. The experiment is repeated some days later under the same circumstances. Three curves of normal young persons are recorded in chart 1.

Usually the elevation of the blood pressure is of short duration; the hypertension due to labor usually varies from 15 to 26 mm. (according to the Riva-Rocci sphygmomanometer), and lasts usually from two to three minutes. It is regularly followed by a slight decrease to below the normal pressure.

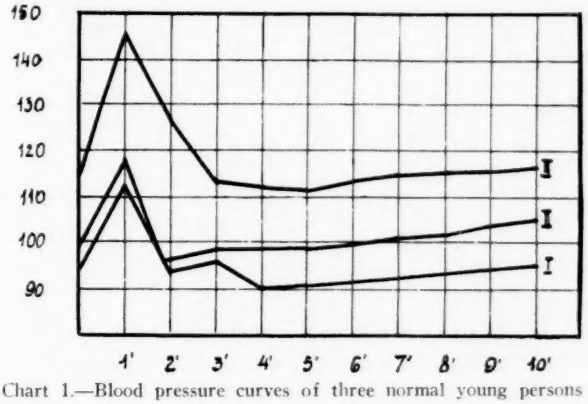

Chart 1.—Blood pressure curves of three normal young persons after labor test.

I believe that determination of the blood pressure curves after the patient has performed physical work gives a reliable method for testing the function of the regulating mechanism of the blood pressure.

PSYCHIC REACTION OF THE BLOOD PRESSURE

Psychic excitement often produces an elevation of blood pressure, as the experiments of numerous authors have demonstrated. The increase in the blood pressure varies from 10 to 40 mm., according to the intensity of the excitement. The important rôle of psychic factors in the pathogenesis of arterial hypertension, therefore, must be taken into consideration. Emotions of long duration may often cause a more or less permanent elevation of the blood pressure level, as described in various papers dealing with the hypertension.

The simple test I have worked out for the determination of the psychic reaction of the blood pressure is as follows: In the early morning hours, repeated measurements are made of the blood pressure, while

the patient is kept in complete physical and psychic rest. Then he is told that he is going to receive an intravenous injection which will be a little painful. A slight elevation of the blood pressure usually follows this declaration.

We give then 1 cc. physiologic sodium chloride solution intravenously, in consequence of which the blood pressure increases rapidly; the highest level is reached just after the injection (within two minutes), and then there is a slight but rapid decrease. In normal persons, the elevation of the blood pressure amounts to from 8 to 15 mm., as measured by the Riva-Rocci sphygmomanometer. Three curves of normal young persons are presented in chart 2.

The form of these curves is subject to many variations, depending on the excitability of the patient; hence, they must be interpreted with great caution. In pathologic conditions, however, they may be of great diagnostic value.

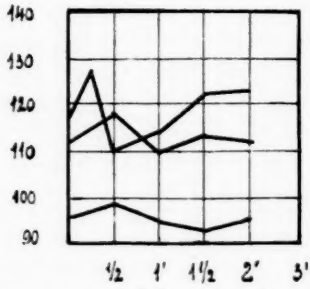

Chart 2.—Blood pressure curves of three normal young persons after psychic test.

PRESENILE FLUCTUATION OF BLOOD PRESSURE

The systolic pressure of persons, aged from 45 to 55, in my country is usually from 110 to 140 mm., as determined by the Riva-Rocci sphygmomanometer in a large series of cases. These values were recorded in the early morning. They must be regarded as a little elevated, the normal values in young persons being somewhat less (usually about 100 mm.). A striking diurnal fluctuation of the blood pressure often occurs in the presenile period. A comparison of the blood pressure measurements made early in the morning and with those made during the day or evening shows the changes illustrated in chart 3.

This inconstancy of the blood pressure is similar to that found in the patients suffering from essential hypertension who were described in the papers of Fahrenkamp [7] and Kylin.[8] The majority of my patients,

8. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

however, apparently were healthy. Only a few of them had the symptoms described by Wenckebach in his report on the "50 years old man" —headache, dizziness, precordial uneasiness, palpitation, etc.

It has been a common observation in the roentgen-ray examination in my patients, that the majority of elderly men have a distinct enlargement of the aorta, often without any sign of cardiac disturbance. In some cases, however, the foregoing slight symptoms were probably caused by aortic alterations, especially in persons who had worked excessively or had led a hurried, worried life.

LABOR TEST IN PATIENTS OF PRESENILE AGE

The most important disturbance in the regulation of blood pressure can be detected by means of the new methods described previously.

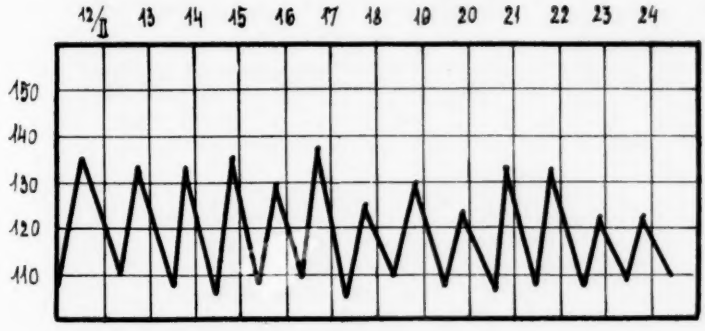

Chart 3.—Comparison of blood pressure measurements made in early morning with those made during the day or evening.

These tests show that the fluctuation of the blood pressure in elderly persons is caused chiefly by a diminished compensating power of the regulating mechanism. In this way, the otherwise transitory elevations may become permanent.

Determinations of blood pressure curves after work has been performed show remarkable differences in elderly and in young persons. This is pictured in the curves of older persons in chart 4 and in the normal curves of young persons in chart 1.

In examining the three curves in chart 4, one finds that the first difference is in the descending portion of the curves. The duration of the elevation of the blood pressure is much longer than it is in younger persons, so that the blood pressure reaches its former level later. The descending portion of the curves is elongated. Contrary to observations in the reaction type of young persons, the elevation of the blood pressure is not only of longer duration but also much higher. The increase of the

blood pressure is between 30 and 60 mm., as determined by the Riva-Rocci sphygmomanometer, and it lasts longer than from three to five minutes. Moreover, subnormal pressure was not found after the elevation as it is in younger persons. Latent disturbance of the regulating mechanism of the blood pressure thus becomes evident as a result

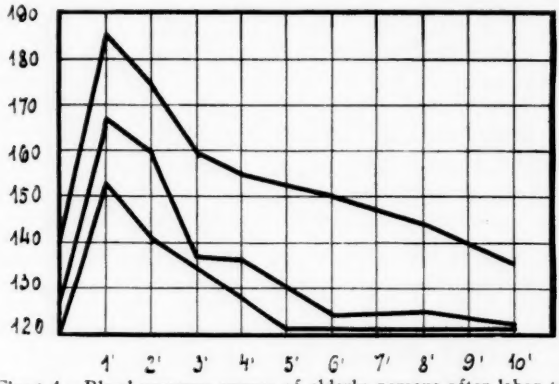

Chart 4.—Blood pressure curves of elderly persons after labor test.

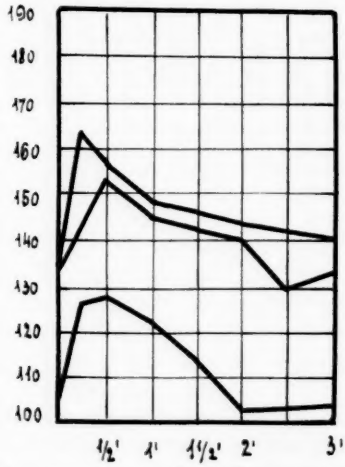

Chart 5.—Blood pressure curves of elderly persons after psychic test.

of the labor test. The compensating powers, which in young persons cause the transitory elevation of the blood pressure to return rapidly to the normal level, are deficient in the presenile period; they act slowly and late. This behavior of the blood pressure curves is an important sign of beginning disturbances of the regulating mechanism.

PSYCHIC TEST IN PATIENTS OF PRESENILE AGE

Conclusions similar to those drawn from the curves obtained in labor tests may be reached in an examination of the curves obtained after psychic excitement. The results in chart 5 should be compared with those in chart 2.

Again one notices a difference in the intensity and duration of the elevation of the blood pressure. The elevation may be as high as from 35 to 40 mm., as measured by the Riva-Rocci sphgmomanometer, and disappears later than it does in young persons. Moreover, the curves may become flat and plateau-like. These curves show, in addition, the deficient compensating power of the regulating mechanism. This can be regarded also as an initial sign of an inclination to hypertension in elderly persons.

In some cases I have observed that the labor test brought out a latent disturbance of the regulating mechanism, while the psychic reaction was of normal type. By means of these methods, it may be possible to separate various types of disturbances of the blood pressure, one of which may be due purely to psychic disorder.

CONCLUSIONS

The blood pressure in persons of presenile age is fluctuating and has a tendency to rise intensively after various irritations. The regulating mechanism of blood pressure is becoming insufficient. Hypertension after the performance of work or after psychic excitement is of a markedly longer duration in older than in younger persons, and diminution in the elevation of the blood pressure follows slowly. In this respect, the behavior of elderly persons is similar to that of persons suffering from arterial hypertension.

The psychic test gives valuable evidence of the important rôle of psychic factors in the pathogenesis of arterial hypertension. The beginning incompetency of the regulating apparatus gives the basis for the eventual persistence of temporary elevations of blood pressure, which are otherwise rapidly compensated for by a well working regulating mechanism.

Usually, labor and psychic tests give the same results, but discrepancies sometimes occur.

THE VALUE OF THE DIAZO TEST ON BLOOD*

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This paper is a report of a study of the blood diazo test and of the conclusions deduced. Blotner and Fitz,[1] the first workers in this country, reviewed the papers of Andrewes[2] and Hewitt[3] of England, of Becher[4] of Germany and of Rabinowitch[5] of Canada. Their work and the recent publication of the studies of Patch and Rabinowitch[6] have been reviewed by us.

Andrewes,[2] while performing the van den Bergh test for bilirubin in the blood, noted a deviation from the normal color. He then added alkali to the end-product and obtained a pink coloration instead of the green of azobilirubin; this occurred only in persons with markedly damaged kidneys. He also found a blood bilirubin less than normal in amount in the same patients. Van den Bergh[7] recognized a hypobilirubinemia in chronic nephritis. Beth,[7] another German worker, differentiated malignant nephrosclerosis from chronic nephritis by the hyperbilirubinemia present in the former, as contrasted with the low level of bilirubin in the latter. Andrewes found the diazo test positive only in those persons having at least 220 mg. of urea (103 mg. urea nitrogen) per hundred cubic centimeters of blood. He waited twenty-four hours after blood was withdrawn before performing the test. This procedure, in our opinion, permitted the disintegration of the small amount of bilirubin present which might interfere with the test.

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* From the Biochemical Laboratories of the Lebanon Hospital, New York.

1. Blotner, H., and Fitz, R.: The Diazo Test in Nephritis, J. A. M. A. **88**: 985 (March 26) 1927.

2. Andrewes, C. H.: An Unexplained Diazo—Color Reaction in Uremic Sera, Lancet **1**:590 (March 22) 1924.

3. Hewitt, L. F.: The Diazo Reaction in Uremic Sera, Biochem. J. **19**:171 (Feb.) 1925.

4. Becher, E.: Die Diazo und Urochromogenreaktion in Blutfiltrat bei Niereninsufficienz, ihre Erklarung und klinische Bedeutung, Deutsches Arch. f. klin. Med. **148**:10 (July) 1925.

5. Rabinowitch, I. M.: Observations on the Value of the Diazo-Color Reaction in the Differential Diagnosis of Uremia, Canad. M. A. J. **15**:725 (July) 1925.

6. Patch, F. S., and Rabinowitch, I. M.: Urea and Creatinine Contents of the Blood in Renal Disease: A Statistical Analysis of Five Thousand Observations, J. A. M. A. **90**:1092 (April 7) 1928.

7. Quoted by Andrewes (footnote 2).

TABLE 1.—*Cases Showing Positive Diazo Test*

Name	Sex*	Age	Clinical Diagnosis	Date	Urea Nitrogen	Non-protein Nitrogen	Creatinine	Phenol-sulphon-phthalein Test	Blood Pressure	Duration of Reaction in Minutes	Comment
1. D. R.	♀	72	Hypertension, chronic nephritis, pyonephrosis	5/17/27	103	145	6.3	.....	120/80	12	Died of heart failure; no signs of uremia at any time
					52	85	3.3	.....	.....	2	
					43	62	3.8	.....	.....	2	
					43	62	2.9	.....	130/70	2	
					43	63	2.4	.....	.....	0	
				7/21/27	49	83	4.0	<5%	.....	0	
2. X.	♂	11	Acute nephritis	.....	...	180	13.0	.....	.....	2½	Died in uremia
3. S. F.	♀	41	Hypertension, prolapse of uterus and of vaginal walls	6/23/27	15	33	....	.....	172/114	1	No signs of uremia at any time; now alive; blood pressure 165; dizziness and spots before eyes
				6/24/27	13	29	1.8	.....	136/ 90	½	
4. G. R.	♀	33	Parturition, chronic nephritis, acute suppression of urine, uremia	8/22/27	...	...	....	.....	145/ 85	...	Acute urinary suppression immediately postpartum; decapsulation of both kidneys three days later; now alive; no symptoms of uremia
				8/23/27	14	29	....	.....	180/104		
				8/24/27	19	40	1.8	.....	155/ 94		
				8/25/27	31	59	3.1	0	154/ 96		
				8/26/27	82	91	4.7				
				8/28/27	35	68	6.1	.....	158/ 90		
				8/30/27	76	110	8.2	.....	166/ 60		
				9/ 3/27	80	120	8.9	.....	150/ 60		
				9/ 9/27	80	127	14.1				
				9/19/27	52	92	8.1	....	.....	3½	
				9/26/27	68	95	6.1	.....	152/ 48	¼	
				10/ 3/27	55	88	5.2	.....	.....	2½	
				10/11/27	40	63	4.9				
				10/19/27	38	69	4.2	.....	134/ 90		
				10/28/27	37	57	4.9	.....	.....	0	
				3/25/28	36	52	3.3	<10%	.....	0	
5. H. M.	♂	56	Prostatic hypertrophy, chronic nephritis urinary retention	1/26/28	123	140	9.1	.....	.....	1	Cystotomy; now living
					132	145	9.8	.....	.....	½	
					85	95	4.2	.....	.....	¼	
				2/26/28	46	74		.....	.....		
				4/16/28	64	72	3.0	.....	.....	0	
6. Y.	♀	65	Chronic nephritis, myocardial degeneration	.....	103	125	7.3	.....	.....	2	Died of heart failure
7. J. C.	♂	45	Acute cholecystitis, urinary retention	3/19/28	145	157	7.1	.....	.....	1½	Patient entered with slight hiccup; no other signs of uremia; now living
				3/21/28	36	64	2.3	.....	.....	0	

* In this column, ♂ indicates male; ♀, female.

Hewitt [3] improved Andrewes' technic in that he heated the reaction mixture instead of waiting twenty-four hours. The heat probably destroyed the bilirubin present. In his series of cases, the diazo test was positive when the urea averaged 366 mg. (170 mg. urea nitrogen) per hundred cubic centimeters of blood.

Finally, Rabinowitch [5] added to the work by noting the accompanying creatinine. A positive diazo test was obtained in cases in which the urea nitrogen was as low as 71 mg. and the creatinine 3.84 mg. per hundred cubic centimeters of blood. He concluded that a positive reaction was

TABLE 2.—*Cases in Which There Appeared Clinical Signs of Uremia or High Blood Nitrogen Values or Both, with a Negative Diazo Test*

Name	Sex*	Age	Clinical Diagnosis	Urea Nitrogen	Non-protein Nitrogen	Creatinine	Comment
1. S. C.	♂	65	Hypertrophy of prostate	72 73	108 125	6.0 4.6	Alive
2. S. D.	♂	71	Hypertrophy of prostate, acute uremia, bronchopneumonia	80	100	2.4	Died
3. I. K.	♂	43	Nephrolithiasis.....	43	85	6.7	Alive
4. M. R.	♂	69	Hypertension, chronic nephritis, acute uremia	51	68	3.3	Died
5. F. L.	♀	70	Acute nephritis, acute uremia	98	125	2.4	Died in coma
6. A. I.	♀	27	Lobar pneumonia.....	58	89	2.2	Alive
7. P. T.	♂	84	Ileus, acute uremia.....	66	97	...	Died in coma
8. I. S.	♂	20	Streptococcus hemolyticus septicemia	43	73	3.8	Died
9. M. W.	♂	61	Uremia, cardiac decompensation	60	86	2.7	Died in coma
10. H. S.	♀	27	Bichloride poisoning.....	72	110	7.9	Died
11. A. H.	♀	57	Diabetes mellitus, chronic nephritis, uremia	140	170	4.6	Died in coma
12. R. A.	♀	9	Acute nephritis, acute uremia	..	40	1.8	Alive
13. F. L.	♀	55	Chronic nephritis, acute uremia	49	76	1.5	Died in coma
14. M. K.	♂	38	Bronchopneumonia, chronic nephritis, uremia	157	200	6.0	Died

* In this column, ♂ indicates male; ♀, female.

seen in patients with definite uremia, and that it was not always associated with a fatal termination (one case). It was also thought that the test might be of greater prognostic significance in chronic nephritis than the determination of the blood creatinine values.

In a series of cases reported by Blotner and Fitz,[1] no case in which the urea nitrogen was below 28 mg. per hundred cubic centimeter of blood showed a positive diazo test. They believed a positive reaction to be of grave significance, as twenty-eight of their thirty-six patients had died within one year. According to them, the test was valuable in the differentiation of uremic coma from coma of other origin.

In the present study, the diazo test was performed in the manner described by Hewitt, plasma being used chiefly. The test was performed

as a routine on 415 consecutive blood specimens collected in the wards of the Lebanon Hospital, and then in 40 more selected cases in which clinical observations or chemical examination of the blood indicated severe damage to the kidney.

In all, seven patients gave a positive diazo reaction of the blood. Of these, four are now living, and their general condition has improved. The positive reaction seemed to follow the level of creatinine rather than that of the other nitrogenous components of the blood. Contrary to the observations of some of the other workers,[6] a positive reaction was obtained in specimens having a creatinine value as low as 1.8 mg. per hundred cubic centimeters of blood. Unlike these workers, we have found the test negative on samples of blood containing more than 3 mg. of creatinine per hundred cubic centimeters of blood. The highest creatinine figure with a negative diazo test was 7.9 mg. per hundred cubic centimeters.

A study of table 2 warrants the statement that the diazo test is not always positive in cases in which there are clinical and laboratory signs of uremia. This holds true even of patients in uremic coma, and does not support the view that the positive diazo test is a means of differentiating uremic coma from coma of other origin.[1]

The claim has been advanced that the diazo test is not positive in cases of nitrogen retention due to obstruction of the kidney. In case 7 in table 1 (patient J. C.), there was a positive reaction which became negative on relief of the obstruction, even though the nitrogen values remained high.

SUMMARY

1. Seven cases showed a positive diazo test. Four of these patients are now living and their general condition has improved.

2. The diazo test is not positive in all cases showing coma or other evidence of a severely damaged kidney.

3. The positive diazo test does not always differentiate uremic coma from coma of other origin.

4. No definite creatinine value can be established as the point at which the positive diazo reaction appears.

5. The determination of the amount of creatinine present is of greater value than is the diazo test in estimating the extent of damage to the kidney.

6. The diazo test may be positive in cases in which there is obstruction of the kidney.

7. If the diazo test is to be performed, it should be done as a routine regardless of clinical signs or blood nitrogen values on the blood of patients whose kidneys are believed to be damaged.

FUNCTIONAL INSUFFICIENCY OF THE SUPRARENAL GLANDS *

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Since the description by Addison, in 1855, of the disease that bears his name, many articles have been written on dysfunction of the suprarenal glands, and many cases have been reported that have shown the picture of insufficiency of these glands as described by him. Most of the autopsies reported have shown destruction of the suprarenal tissue by tuberculosis, tumor, hemorrhage, acute infection, thrombosis or some other direct-acting agency. Investigators have also described an enlargement, loss of pigment and disappearance of the medulla of the gland in wasting diseases, particularly in diseases due to inanition and dietary deficiencies (vitamins). It is not necessary to review the mass of literature in detail, since it is summarized in the articles here cited.[1]

The purpose in this article is to point out a type of suprarenal insufficiency frequently seen in certain regions, which seems to be associated with definite climatic factors, and which responds well to the administration of epinephrine orally. I wish also to point out the close similarity of the symptoms and observations in several of these cases to those in peptic ulcer, chronic appendicitis and tuberculous enteritis and to emphasize the importance of considering dysfunction of the suprarenal glands in the differential diagnosis of such disturbances of the gastro-intestinal tract.

Natives of the cooler portions of the temperate zone who take up residence in the tropics frequently become subject to disturbances of the gastro-intestinal tract and to a general loss of vitality and vigor which seriously impair their usefulness and necessitate frequent and expensive home leaves for recuperation. These disturbances often occur during the first year of residence in the tropics, but they may not appear for several years. The principal gastro-intestinal symptoms are a tendency to diarrhea (in most cases without the presence of pathogenic organisms in the stools), achlorhydria or hypochlorhydria with impaired digestion and hypermotility of the whole tract. Spasticity of the cardiac, pyloric or ileocecal sphincter is often present. These disturbances are usually

* From the Department of Medicine, Peking Union Medical College.

1. Reisman, David: Oxford Medicine, London, Oxford University Press, 1921, vol. 3, p. 783. McCarrison, Robert: Studies in Deficiency Disease, London, Oxford University Press, 1921. Biedl, Arthur: Internal Secretory Organs, New York, William Wood & Co., 1913.

accompanied by a fall in blood pressure, anemia, loss in weight and progressive weakness and lassitude. Tropical sprue is probably only an exaggeration of this condition. Vascular hypotension and lowered basal metabolism have been observed in many tropical and subtropical countries, but so far no one has found an explanation for the condition. Dietary differences have been suggested as the cause of these changes, but foreigners in the tropics eat much the same kinds of food as they do in their home lands. In New Orleans it was found that, although the basal metabolic rate is subnormal, the average caloric intake is about the same as in cooler latitudes.[2]

Northern China, Korea and Japan are far removed from the tropics, and yet the same body disturbances as occur in foreigners in the tropics are met with here to an almost equal extent. The native people of Northern China also show the same subnormal metabolism and hypotension as are seen in both foreigners and natives living in the tropics. Tung [3] has shown that Americans coming to Peking and Chinese students returning after several years in America, all exhibit a definite drop in both systolic and diastolic blood pressure after a few years of residence in this country. This observation of tropical effects so far north has led to much speculation concerning the cause. The mean yearly temperature in China is practically the same as that of similar latitudes in the United States, where few such disturbances are seen. The most striking resemblance of this climate to that of the tropics is the occurrence of the rainy season during the period of most intense summer heat. At one time in July, 1927, the temperature was 114 F. in the shade, with a relative humidity of 92 per cent!

The accompanying charts showing the mean monthly temperature and relative humidity in Peking for several years were prepared by Dr. H. Necheles from data published in the *Peking Union Medical College Weekly Bulletin*. The third chart, showing the average monthly rainfall in Peking and Shanghai from 1900 to 1917, was prepared by Dr. A. M. Dunlap and published in the aforementioned bulletin, May 6, 1924. From these three charts, it is seen that June and July are the two warmest months and that the relative humidity and rainfall show sharp maxima coinciding with the maximum heat. During this period of intense heat and high humidity, the heavy rainfall affords little relief from the oppression. There is also little difference in the day and night temperatures, so that cooling of the body remains difficult at all times for a period of about six weeks. This same type of rainy season during the summer is met with throughout Northern China, Korea and Japan.

2. Borgstrom, P.: Am. J. Physiol. **79**:221, 229, 237, 242 and 245, 1926.

3. Tung, C. L.: Relative Hypertension of Foreigners in China, Arch. Int. Med. **40**:153 (Aug.) 1927; Chinese J. Physiol., 1928, vol. 2.

I believe this yearly period of simultaneous high heat and high humidity to be the factor responsible for the disturbances of body function seen in the tropics and in those other regions having the rainy season during midsummer. In a surprising number of instances, the first history of body disturbance dates from this season, often from the first period of this kind encountered by the patient if he is a foreigner.

I am, of course, excluding from consideration those parasitic and bacterial diseases so frequent in the tropics. That they may be eradicated by proper hygienic precautions was strikingly illustrated in the Panama Canal Zone by Gorgas. It is recognized by many who are familiar with tropical conditions that, even with all such parasitic diseases excluded, there still will exist functional disability of such

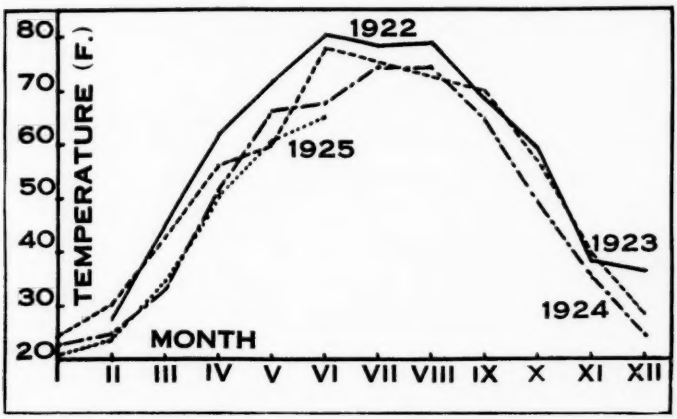

Chart 1.—Chart showing the mean monthly temperature in Peking from 1922 to 1925.

frequency and severity as seriously to impair the efficiency of workers there. It is this disturbance that I believe is caused by the hot, humid season when cooling of the body becomes extremely difficult.

The level of the production of heat under basal conditions seems definitely associated with the function of the thyroid gland, but above this level, the suprarenal glands appear to be responsible for the stimulation of the production of heat. It has been demonstrated [4] that secretion of epinephrine increases in animals as the bodily activity or loss of heat is increased, while Boothby and Sandiford [5] showed that the injection of epinephrine caused a marked increase in the production of heat.

4. Cannon, W. B.: Am. J. Physiol. **79**:466, 1926. Hartman, F. A., and Hartman, W. B.: Ibid. **65**:612, 1923.

5. Boothby, Walter M., and Sandiford, Irene: Am. J. Physiol. **66**:93, 1923.

Sundstroem [6] has shown that rats produce considerably less heat when kept in hot, moist air than under ordinary conditions, and that this depression is greatest when the air is not in motion. Cramer [7] found marked changes in the suprarenals in mice kept in a temperature of from 37 to 38 C. for several days, the principal change being a loss of the characteristic lipoid from the cortex, which he interpreted as evidence of inhibition of function. It seems, therefore, that the difficulty of keeping cool in the hot humid season, wherever it occurs with sufficient intensity, serves to cause a marked suppression of suprarenal function, with the result that diarrhea and other disturbances of the gastro-intestinal tract appear on slight provocation. From the histories of the cases

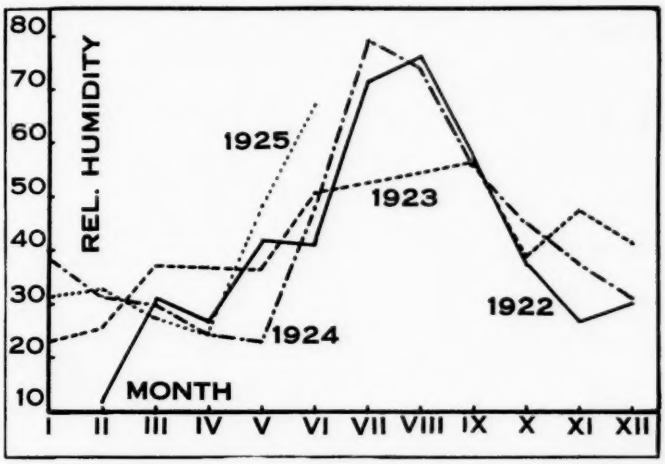

Chart 2.—Chart showing the monthly mean of the relative humidity in Peking from 1922 to 1925.

herein reported it would seem that this suprarenal depression is often so severe that function is not regained spontaneously, but may be brought about through a course of epinephrine therapy.

During the four months that have elapsed since I began this study, about forty cases of apparent suprarenal insufficiency have been encountered. A few of these were lost track of before definite results could be obtained. At present, the number of such cases seen each week is rapidly increasing as various manifestations become more familiar. As time passes, the impression grows stronger and stronger that this condition

6. Sundstroem, E. S.: J. Biol. Chem. **63**:xli (proceedings) 1925; Physiol. Rev. **7**:320, 1927.

7. Cramer, W.: Brit. J. Exper. Path. **7**:88 and 95, 1926.

is probably responsible for a great amount of the ill health in regions in which the maxima of heat and moisture coincide. Nor is it a disease peculiar to foreigners in these regions, since many of my patients are Chinese. Interestingly enough, all my patients have been adults, which agrees with the observations of Sundstroem that the depressing effect of moist heat (on rats) was evident only in adult life. Aballi,[8] however, has described two cases in patients 2 days and 5 months old, respectively, which occurred in Cuba.

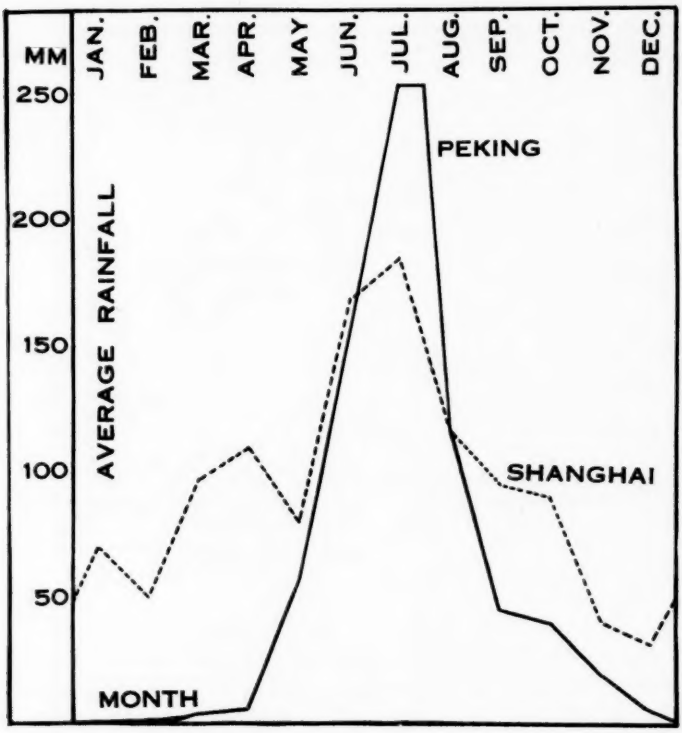

Chart 3.—Chart showing the average monthly rainfall in Peking and Shanghai from 1900 to 1917.

I have not had an opportunity to determine how many infants and children with summer gastro-intestinal disturbances, seen in all countries would be benefited by epinephrine therapy.

I shall present the histories of a few of the more typical cases in some detail, and briefly summarize the remainder in order to conserve space.

8. Aballi, A.: Rev. méd. cubana **33**:15, 1922.

REPORT OF CASES

CASE 1 (Hosp. no. 18864).—*History.*—A Chinese woman, aged 25, married, was admitted to the hospital on Dec. 31, 1927. In January, 1927, her first and only pregnancy terminated in normal labor. The child was breast fed; the mother was strong and healthy. In June, she began to feel ill, complaining of a hot sensation in the chest and a dull aching in both lumbar regions. In August, she began to notice swelling of the feet, which gradually included the legs, abdomen and finally the face (in October). Fever and chilliness were present for the first two weeks, and the output of urine was markedly diminished. The movement of the bowels was irregular; sometimes there were four or five watery movements a day and again only one movement in from two to three days. In August, the child died of "cholera"—severe diarrhea. The patient's condition grew worse until October, when there was edema of the whole body, marked loss of appetite, general malaise and weakness. After October the swelling gradually subsided, but epigastric discomfort, vomiting and irregularity of bowel movements became worse. Two weeks before admission to the hospital, she again became feverish and noticed dyspnea and palpitation of the heart.

The past history was irrelevant except regarding menstruation. This began at the age of 17, the period being forty ± days apart and accompanied by considerable pelvic pain. The patient had not menstruated since childbirth in January, 1927.

Physical Examination.—The principal points shown by the examination were: marked emaciation, dry, loose and scaly skin, edema of the feet and legs, abdomen somewhat doughy to palpation, lungs and heart normal and a blood pressure of systolic 76 and diastolic 50. The urine contained a trace of albumin but no casts. The phthalein output was normal. The blood showed moderate anemia (3,300,000 erythrocytes and 70 per cent hemoglobin). X-ray and fluoroscopic examination of the chest and gastro-intestinal tract did not show any abnormalities. Gastric analysis with an Ewald test meal demonstrated achlorhydria both before and after the intake of food and freedom from lactic acid. A dextrose tolerance test, using 100 Gm. of dextrose orally, gave the following readings for the blood sugar: fasting, 95.5 mg. per hundred cubic centimeters; half an hour after the administration of dextrose, 125 mg.; one and a half hours after, 111 mg., and three hours after, 100 mg. The stools did not contain parasites or ova. The Wassermann test of the blood, the Widal and the Weil-Felix tests were negative. The basal metabolic rate was minus 9 per cent (Tissot apparatus).

Treatment and Course.—During the first ten days in the hospital, the patient lost 6 pounds (2.7 Kg.) in weight, and appeared to have a grave prognosis. She was extremely weak, with poor appetite, and had a continuous dull pain in the loins. The edema disappeared during this time, which probably accounts for much of the loss in weight. She was then given 1 mg. of epinephrine orally before each meal. The pain in the lumbar region ceased within a day, the appetite improved, and the patient gained 9 pounds (4.1 Kg.) during the next week. The administration of epinephrine was then discontinued for the purpose of study, the pain in the lumbar region recurred for one day, and the patient lost 3 pounds (1.4 Kg.) during the succeeding three days. During the next three weeks, when she was not given any medication, she slowly gained 2 pounds (0.9 Kg.) and felt fairly well. Epinephrine was then again given, 1 mg. daily before breakfast, and she gained 4 pounds (1.8 Kg.) during the succeeding week. The patient is still under observation. The blood pressure has risen from 76 systolic and 50 diastolic to 94 systolic and 68 diastolic.

I present this case in detail because it is so clearcut and striking. The history of asthenia, emaciation, and pain in the lumbar region, the disturbances of the gastro-intestinal tract, achlorhydria, vascular hypotension, high degree of dextrose tolerance and the marked response to epinephrine combine to give a clearcut picture of suprarenal insufficiency. Tuberculous enteritis or peritonitis was suspected on admission, but supporting evidence was not obtained.

CASE 2 (Hosp. no. 18,922).—*History.*—A Chinese man, a student, aged 24, was admitted to the hospital on Dec. 19, 1927, complaining of diarrhea since May, 1927, with great weakness and loss in weight. He came as a student from Shansi to Peking three years previous to the time of admission. Each summer during his stay in Peking he had had severe diarrhea, with bloody and mucous stools. The blood and mucus disappeared each time after about ten days, but since the attack in May, the bowel movements had continued from three to four times a day; they were watery, but were not accompanied by pain. He had had occasional attacks of nausea without vomiting. Ten days before admission, he began to cough and expectorate a whitish sputum. There was no fever. The appetite was entirely gone, and the patient was too weak to stand alone.

Physical Examination.—Marked pallor and emaciation, with pitting edema of the feet, were present. The abdomen was full, tense and doughy. The lungs and heart were normal. The blood pressure was 92 systolic and 50 diastolic. The urine showed a faint trace of albumin. There were 3,000,000 red cells with 50 per cent hemoglobin. The number of white blood cells was normal. X-ray examination showed that the chest was normal. X-ray and fluoroscopic examination of the gastro-intestinal tract showed retention in the stomach and retention and dilatation in the ileum suggesting adhesive peritonitis (tuberculous?). The results of examinations of the stool, the Wassermann, Widal and Weil-Felix tests were all negative. The clinical impression was that the patient had tuberculous enteritis or peritonitis or both.

The course of the patient was rapidly downhill; he had fever, dehydration and diarrhea. He died on the sixth day after admission.

Autopsy.—Autopsy, performed by Dr. J. R. Cash, showed some evidence of bronchopneumonia of recent date and marked atrophy of the viscera, especially of the heart and liver, but the suprarenal glands were slightly enlarged and softer than normal. On section, the cortex appeared pale, yellowish gray and was somewhat translucent. Near the edges of the suprarenals, the medulla was represented by a thin brown line to which the opposing layers of cortex were adherent. In the central portion of the glands, the medulla had become softened in large areas. Sections made midway between the center and the poles of the glands revealed the medulla to be thick, pale gray and showing a thin line of softening next to the cortex. There was no evidence of tuberculosis anywhere in the body. The peritoneum was normal, as was also the gastro-intestinal tract, except for atrophy. No local cause could be found for the diarrhea.

The principal value of this case is in the report on the autopsy. The clinical and x-ray impressions were that tuberculous enteritis or peritonitis was the cause of death, although, on looking back, the similarity to semiacute suprarenal insufficiency can be seen. The patient was not seen by me. The lack of any pathologic changes to account for the

patient's condition, other than those in the suprarenal glands, seems to justify the diagnosis of suprarenal insufficiency with a terminal bronchopneumonia.

CASE 3 (Hosp. no. 19,133).—*History.*—A Chinese girl, aged 15, was admitted to the hospital on Jan. 12, 1928, complaining of irregularity of menstruation, with profuse and prolonged bleeding. Menstruation began in March, 1925. There were four periods in 1926 and one in May, 1927. The last one began about December 15 and was still continuing at the time of admission. Except for the last period, the duration was about a week, with profuse bleeding but without pelvic or abdominal pain.

About two months before admission, the patient noticed some pallor. Since December 15, she had been weak and for the last ten days had been troubled with dizziness and loss of appetite and weight. There was no history of other bleeding or ailments, except constipation for several months previously. She came from Hunan to Peking in 1925.

Physical Examination.—Rather marked pallor, slight emaciation, a soft blowing systolic murmur heard over the whole heart, and a blood pressure of 94 systolic and 60 diastolic were present. The red blood cells numbered 2,340,000, with 35 per cent hemoglobin. The white cell count was normal. Urinalyses revealed a normal urine. X-ray examination of the chest showed the lungs clear and the heart 15 sq. cm. undersize.

Treatment and Course.—On the basis of the menstrual history, hypotension and constipation, with negative physical observations, the diagnosis of suprarenal insufficiency was made, and epinephrine was given orally. On January 16, the patient received 1 mg. before each meal, which resulted in a marked lessening of the bleeding on that day and on the succeeding one. On January 18, she began to receive 1 mg. daily before breakfast. On the next day, the bleeding completely ceased and did not recur during the patient's stay in the hospital. On January 20, the red cell count had risen to 3,710,000, with 45 per cent hemoglobin. The patient was discharged on January 22, to be followed in the outpatient department.

CASE 4 (Hosp. no. 18,585).—*History.*—A Chinese man, aged 37, was admitted to the hospital on Nov. 12, 1927, complaining of epigastric pain for the past year. One year previous to the time of admission, he attended a banquet and drank a great deal of wine. An hour and a half later he became nauseated, had epigastric and abdominal pain, and noticed profuse sweating and trembling. The next morning a tarry stool was passed, and pallor of the face and lips was present. In two days, he became better, but he has since suffered from a dull pain in the right hypochondrium. In September, this pain grew worse, culminating in another severe attack on November 7. There were three spasms of pain during the day, each lasting from five to fifteen minutes. He became nauseated but did not vomit. The stools of the next three days were tarry.

Physical Examination.—The results of the examination were normal, except for moderate obesity and the presence of small hemorrhoids. The blood pressure was 102 systolic and 74 diastolic. Gastric analysis before and after an Ewald test meal showed free acid of 58 and 79. Examination of the blood, urine and stool gave normal observations. X-ray examination of the gastro-intestinal tract did not show any abnormality, except some stasis in the lower part of the ileum.

Treatment and Course.—A tentative diagnosis of duodenal ulcer was made by the attending physician, but with the idea that the condition might be purely a

functional disturbance, the administration of epinephrine, 1 mg. twice daily, was begun on November 19. Up to this time the patient had been having a great deal of abdominal pain and was constipated. Within two days after the administration of epinephrine was begun, the pain ceased, and the bowel movements were normal. The epinephrine therapy was discontinued November 28, and when last seen December 16, the patient was still free from pain and was having normal bowel movements.

The clinical diagnosis of duodenal ulcer was plausible in this case, but as complete relief was obtained by the use of epinephrine, the condition must be considered functional rather than organic. Acute spasm of the pyloris must have occurred at the time of the attacks, causing congestion of the mucosa and hemorrhage.

CASE 5 (Hosp. no. 19,162).—*History.*—A Russian, aged 26, was admitted to the hospital for study on Jan. 14, 1928, complaining of obstinate constipation since October, 1924. He came to China from Siberia in 1923, and the next fall (October, 1924) began to be constipated, although otherwise well. The use of cathartics caused a great deal of pain in the right lower quadrant of the abdomen. He complained of slight abdominal pain early each morning. The results of physical and x-ray examinations were negative, except that some tenderness of the sigmoid colon was noted. The blood pressure was 106 systolic and 66 diastolic. The blood, urine and stools were normal. A dextrose tolerance test, using 100 Gm. of dextrose, gave 95.5, 153.8, 133.3 and 80 mg. per hundred cubic centimeters of dextrose, respectively, in samples of blood taken during fasting, and half an hour, one and a half hours and three hours later.

Treatment and Course.—The oral administration of 1 mg. of epinephrine daily was begun on January 17, and spontaneous bowel movements started the next day. The patient suffered from acute gastric distress ten minutes after taking the first dose of epinephrine; so the dosage was reduced to 0.6 mg. daily. Word was received from him on February 28 saying that he was normal in all respects, and that he had been without epinephrine for a period of three weeks.

The diagnosis in this case was spastic constipation, beginning shortly after the patient's first summer in China, and showing prompt relief following the use of epinephrine.

CASE 6 (Hosp. no. 878).—*History.*—A Swiss man, aged 39, was first seen by me on Sept. 22, 1927. He had been in poor condition for ten years, suffering from constipation, loss of weight, nervousness, indigestion and general lack of proper vitality. Abdominal and epigastric pain readily followed indiscretions in food. Physical examination did not show any abnormality, except the presence of hemorrhoids. All the various laboratory procedures gave normal results.

Treatment and Course.—On Sept. 22, 1927, the patient began to take 1 cc. of epinephrine (1:1,000) sublingually each day, with the following results: On September 22, the weight was 67.3 Kg. (148 pounds) and the blood pressure was 115 systolic and 70 diastolic. On September 30, he weighed 68.3 Kg. (151 pounds), and the blood pressure was 100 systolic and 62 diastolic. On October 24, the weight was 70.9 Kg. (156 pounds), and on December 6 he weighed 72 Kg. (159 pounds). The blood pressure was then 130 systolic and 80 diastolic; the patient felt well and was full of vitality. The bowel movements had been regular and normal since the onset of epinephrine therapy. On February 11, he was again seen, at which time he weighed 73 Kg.

(161 pounds) and had a blood pressure of 124 systolic and 84 diastolic. After the last preceding visit, December 6, the dosage of epinephrine was reduced gradually to 4 drops daily, and finally on January 18 it was stopped completely. Within three days, the patient began to be constipated and to have a feeling of weakness and collapse. He took 8 drops of epinephrine solution on January 22, and within a day was again feeling normal. This daily dose was again gradually reduced and withdrawn on February 2. Up to the time of this visit, he had felt normal for nine days. The advice given to him is that he abstain from the epinephrine, using it only temporarily in case of need.

The gain of 12 pounds (5.4 Kg.) in the weight of this patient and the general improvement under epinephrine therapy were marked. Of special interest is the steady rise in the diastolic blood pressure to a normal level.

CASE 7 (Hosp. no. 17,923).—*History.*—An American man, aged 46, was admitted to the hospital on Sept. 4, 1927, complaining of severe epigastric and abdominal pain, constipation, weakness and loss in weight. He came to China in April, 1927, landing at Shanghai, where he had had severe diarrhea for a period of four days, without blood or mucous in the stools, but with severe pain. In June, he came to Peking and at once had a similar attack (fifteen bowel movements a day). On August 16, he had still another attack, which was acute and was accompanied by vomiting and severe gastric pain. The diarrhea lasted only one day, after which constipation occurred, but the pain in the stomach persisted. On admission, he complained of substernal pain and a choking feeling after swallowing, of pain in the stomach which was present at all times but which was worse after meals, and of pain in the lower part of the abdomen accompanied by much gurgling. He gave a history of a similar attack of diarrhea with vomiting and gastric pain in 1907 during a visit in Japan. This attack had ceased spontaneously a few weeks after leaving Japan. In 1923, ulcer of the stomach had been diagnosed in America because of the presence of gastric pain and pylorospasm.

Physical Examination.—Results of examination revealed little except that the patient was an intensely nervous and thin person, with a blood pressure of 124 systolic and 76 diastolic. X-ray examination of the chest did not show any abnormality; that of the gastro-intestinal tract showed only marked hyperperistalsis of the stomach. Visualization of the gallbladder by the Graham test was normal. Observations on the blood and urine were normal, except for the presence of a low amount of sugar in the blood during fasting, 66.6 mg. per hundred cubic centimeters. All examinations of the stool gave normal results. The blood pressure showed a tendency to marked decline during the late afternoon if the patient exerted himself much, and at such times severe occipital headache began.

Treatment and Course.—The diagnosis of suprarenal insufficiency, with hypermotility of the gastro-intestinal tract and spasticity of the sphincters was made, and 1 mg. of epinephrine was given sublingually before breakfast each day, beginning on September 8. Within three days the painful peristalsis of the lower part of the abdomen had ceased, and after another two days the cardiospasm and epigastric discomfort were entirely relieved, and the bowels were functioning normally. After eight days of epinephrine therapy, the patient left the hospital and stopped the use of epinephrine. Two weeks later, he returned with the former symptoms and again was completely relieved by the administration of epinephrine. This time he took the drug for three or four weeks. Six weeks later, Oct. 19,

1927, he reported a gain in weight of 20 pounds (9 Kg.) and perfect function of the gastro-intestinal tract without epinephrine therapy. He said that he felt better in general than he had ever felt before in his adult life. He reported similarly in January, 1928.

This case presents the typical picture of suprarenal insufficiency with hypermotility of the entire gastro-intestinal tract and spasticity of the sphincters, and also a tendency to vascular hypotension on exertion instead of the relative hypertension which effort should call forth. The low amount of blood sugar and alternating diarrhea and constipation completed the picture. The relation of the onset of this trouble to the patient's arrival in the Orient is definite. The latter part of April in Shanghai is warm and moist. His worst attack in Peking occurred just at the end of the period of high temperature and humidity.

CASE 8 (Hosp. no. 13,768).—*History.*—An American woman, aged 36, came to China by way of Japan in July, 1927, having been in good health in America. As she approached Japan, hot, humid weather was encountered, and she developed a moderate but continuous diarrhea and edema of the feet and ankles. When she arrived in Peking in July, both the edema and diarrhea grew markedly worse. There was some mucus but no blood in the stools. Pathologic organisms were not found then or subsequently. She felt tired and weak, and complained of cramplike pains in the abdomen. There was some dull epigastric pain and distention, and constant gurgling in the intestines. There was no fever. Physical examination then or later did not reveal any abnormalities. In August, 1924, she had had an attack of giant urticaria following bathing and exposure to the sunlight.

The edema disappeared in the course of two months, the diarrhea improved to from three to four stools daily, and she felt rather normal. Every few weeks exacerbations would occur, especially at the menstrual periods. Another severe attack occurred in September, 1925, after a fatiguing trip into Mongolia during the hot weather.

The family history is interesting in that the father suffers from asthma, and the mother from angioneurotic edema, while the mother's father died of Addison's disease.

On March 11, 1925, gastric analysis revealed achlorhydria; the blood counts were normal and the blood pressure was 112 systolic and 70 diastolic. On May 11, 1926, the number of red cells had decreased from 5,200,000 to 4,550,000, and the blood pressure from 112 systolic and 70 diastolic to 94 systolic and 60 diastolic. There was still complete achlorhydria. The sigmoid colon was easily palpable and thickened. There was marked peristalsis in the lower part of the abdomen. X-ray examination of the chest and gastro-intestinal tract was negative. The blood sugar during fasting at this time was 90 mg. per hundred cubic centimeters. On April 2, 1927, the red cell count had fallen to 4,000,000 per cubic millimeter.

Treatment and Course.—In July, 1927, she had another severe attack of diarrhea with frothy watery stools. She vomited once during this attack. While the attack continued, she was given 0.3 cc. of epinephrine (1:1,000) subcutaneously once a day for five days, and then 0.5 cc. a day sublingually for two weeks. The improvement was immediate and definite, the stools becoming fewer, and the patient feeling much better while the epinephrine was given and for several months thereafter.

In this case, the direct relationship between the onset of trouble and contact with tropical summer weather is again evident. The hyperperistalsis, diarrhea, epigastric discomfort, decrease in blood pressure, edema, achlorhydria and urticarial reaction all point to an insufficiency of the suprarenal glands brought on by the tropical heat.

CASE 9 (Hosp. no. 19,023).—*History.*—A Chinese man, aged 60, was admitted to the hospital on Dec. 30, 1927, complaining of inability to eat solid food for the previous six months. In December, 1926, he had begun to notice some difficulty in swallowing solid food. This had gradually become worse until July, since which time nothing solid had been taken. There had been occasional regurgitation of food before July, and frequently during the last six months. The material regurgitated was always in the same form as when eaten. There was a sense of pressure under the sternum after eating, but no actual pain. There was never blood in the vomitus or stools. The appetite remained good, although there was marked loss in weight because of the limited intake of food. The patient was constipated throughout this period.

Physical Examination.—Examination revealed marked emaciation, arteriosclerosis, a blood pressure of 100 systolic and 70 diastolic, and a moderately enlarged spleen. The observations on the blood and urine were normal. A few entameba cysts and *Ascaris* eggs were found in the stools. The Wassermann test of the blood was negative. X-ray and fluoroscopic examinations showed delay of the barium at the cardia with dilatation and antiperistalsis. There was no filling defect. The cardia was seen to open and discharge barium from six to eight seconds after the patient swallowed, showing that opening was possible. Esophagoscopy did not reveal any pathologic change or new growth, only spasm of the sphincter.

Treatment and Course.—On the basis of the negative observations for organic lesion, and in view of the vascular hypotension and constipation, the patient was given 1 mg. of epinephrine orally before each meal, beginning on January 4. He was put on a full diet on January 7, and did not experience further difficulty in swallowing. The bowel movements became regular and normal two days after the medication was started.

In the table are summarized the principal features of all the cases so far studied, including those presented in detail in the preceding pages. Certain points are apparent in a study of this series of cases.

1. The disturbance affects foreigners in China much more than it does the Chinese. Foreigners constitute almost half in this series, but in this hospital, the total number of admissions of foreign and Chinese patients for 1927 was in the ratio of 1 : 5, so that foreigners must be much more susceptible to this disturbance than are the Chinese.

2. Among the eighteen foreigners studied, the disturbance began in six of them less than one year after their coming to China. In some of these, the relation of onset to arrival in China was so definite that there could be little doubt that the climatic change was responsible.

3. The time of onset of symptoms, when this could be definitely established, was during the summer or fall.

Tabulation of Cases of Suprarenal Insufficiency

Hosp. No.	Nationality	Sex	Age, Years	Time in China Before Onset	Month of Onset	Principal Disturbances	Blood Pressure	Result of Treatment With Epinephrine
18864	Chinese	F	25	Since birth	June	Diarrhea, edema, emaciation, achlorhydria	76/50	Relief at once
18922	Chinese	M	24	Since birth	May	Diarrhea, edema, weakness, emaciation	92/50	No treatment; died
19133	Chinese	F	15	Since birth	Dec.	Menorrhagia, anemia ...	94/60	Relief at once
18585	Chinese	M	37	Since birth	Nov.	Epigastric pain, constipation, intestinal bleeding	102/70	Relief at once
19102	Russian	M	26	1 year	Oct.	Constipation, abdominal pain	106/66	Relief at once
878	Swiss	M	39	5 years	Indefinite	Constipation, weakness, abdominal pain	100/62	Relief in a few days
17923	American	M	46	Few weeks	April	Diarrhea, constipation, cardiospasm, pylorospasm, emaciation, weakness	124/76	Relief in a few days
13768	American	F	36	On arrival	July	Diarrhea, edema, urticaria, weakness, achlorhydria	94/60	Some improvement at once
19023	Chinese	M	60	Since birth	Dec.	Cardiospasm, emaciation, constipation	100/70	Relief at once
19080	Chinese	M	27	Since birth	July	Diarrhea, weakness, constipation, abdominal pain, vomiting, edema	104/64	Relief with rest in bed
19228	American	F	34	1 year	Summer	Constipation, weakness, pain in epigastrium, hypochlorhydria	98/64	Good effect in few days
19120	Chinese	M	25	Since birth	July	Diarrhea, abdominal pain, loss in weight	98/58	No report
19125	Chinese	M	50	Since birth	Dec.	Pylorospasm, constipation, loss in weight, anemia, achlorhydria	120/40	No treatment
18732	American	F	34	5 years	June	Diarrhea and constipation, visceroptosis, hyperistalsis, abdominal distention	100/60	Prompt relief
19167	American	F	36	4 years	May	Diarrhea, headache and fainting	93/58	No report
4986	Russian	M	40	Before coming	.....	Heartburn, epigastric distress, weakness, constipation, hemorrhoids, pylorospasm	100/60	No report
35973	Chinese	F	24	Since birth	Indefinite	Dysmenorrhea, menorrhagia, diarrhea and constipation, epigastric discomfort, vomiting, anemia	100/70	Prompt relief
18753	American	F	38	....	Indefinite	Pain in right iliac fossa, dysmenorrhea, neurasthenia	98/60	Prompt relief
19707	Chinese	M	34	Since birth	August	Abdominal pain and distention; vomiting, diarrhea and constipation, fever and loss in weight	92/54	Prompt improvement
16571	Chinese	M	22	Since birth	Indefinite	Constipation, loss in weight	90/58	Prompt relief
16202	Chinese	F	27	Since birth	Indefinite	Abdominal pain, nausea, vomiting, diarrhea, dysmenorrhea, epigastric pain, headache, fainting	84/56	No effect
13804	American	F	36	9 years	Fall	Nausea, dizziness, headache, dysmenorrhea, constipation	80/50	No report
19602	Chinese	F	49	Since birth	Dec.	Fever, malaise, tetany, epigastric distress, vomiting, emaciation, achlorhydria	70/50	Good effect
19170	Chinese	M	20	Since birth	July	Diarrhea, abdominal pain, loss in weight	86/44	No report

Tabulation of Cases of Suprarenal Insufficiency—Continued

Hosp. No.	Nationality	Sex	Age, Years	Time in China Before Onset	Month of Onset	Principal Disturbances	Blood Pressure	Result of Treatment With Epinephrine
15905	American	F	28	2 months	Dec.	Diarrhea, constipation, epigastric pain	98/65	Good effect
	Chinese	M	50	Onset in U.S.A	Summer	Asthma for 23 years' standing	96/66	No effect
17068	American	M	54	....	....	Diarrhea, abdominal pain, loss in weight, anemia, achlorhydria	94/60	Good effect
18948	Chinese	M	37	Since birth	Aug.	Pylorospasm, vomiting, emaciation, constipation, hypochlorhydria	82/64	No report
16462	Chinese	M	21	Since birth	Sept.	Constipation, abdominal pain, pylorospasm	108/62	Relief at once
18894	Swedish	M	31	5 years	Sept.	Abdominal pain, nausea, constipation, hypochlorhydria	96/62	Relief in a few days
17675	Chinese	M	46	Since birth	Aug.	Severe dysentery, diarrhea persisted for weeks after infection was gone	.....	Cessation of diarrhea at once
18297	Chinese	M	66	Since birth	May	Cardiospasm, heart failure, arteriosclerosis	104/58	Doubtful
17213	American	M	41	4 years	Indefinite	Dull abdominal pain, hyperperistalsis, some constipation, hypochlorhydria	115/72	Prompt relief
18902	Chinese	M	25	Since birth	Summer	Vomiting, weakness, pylorospasm, constipation	110/74	No report
15030	American	F	37	10 years	Indefinite	Epigastric distress, hives, urticaria, pigmented areas of skin	88/56	No report
19285	American	M	35	8 years	June	Indigestion, diarrhea, loss in weight and strength, constipation	100/56	No report
19532	Chinese	F	30	Since birth	Indefinite	Epigastric pain, vomiting, pain in right iliac fossa, constipation	78/30	Prompt relief
8204	American	M	34	1½ years	June	Diarrhea, discomfort in left upper quadrant	80/40	Prompt relief
19817	Chinese	M	32	Since birth	May	Epigastric pain, constipation, undernourishment, intestinal obstruction	74/50	
19803	Russian	F	45	2 months	.....	Epigastric pain, constipation, nausea, vomiting, emaciation, cough, weakness, amenorrhea, achlorhydria	90/50	Prompt relief of symptoms and gain in weight

4. Both sexes are about equally afflicted.

5. The principal symptoms complained of are diarrhea or constipation or both alternating, abdominal and epigastric pain, nausea and some vomiting, weakness and loss of weight, pylorospasm, cardiospasm and anemia. There also occurred urticaria, pigmentation of the skin, edema, menorrhagia and marked vascular hypotension. Both systolic and diastolic blood pressures are, in general, even considerably below the low values so commonly found in China. The blood pressure of the foreigners of this series shows much greater deviations from the normal than does that of the Chinese.

6. In some of the cases, laboratory tests showed hypoglycemia and high tolerance for dextrose. In most of the cases, there was either hypochlorhydria or achlorhydria. In many cases x-ray examination

revealed spasm of the ileocecal sphincter with stasis in the ileum and marked dilation. In such cases, there was usually some tenderness in that region.

COMMENT

This series of cases might be enlarged by further delay in making this report, but I feel that the present number is sufficient to demonstrate the picture of insufficiency of the suprarenal glands. The principal lack, of course, is in the scarcity of autopsy reports. This will, no doubt, be remedied in time after attention has been directed to the suprarenal glands. Another important feature of the study of this disturbance will be the observation of treated patients during the coming summer and fall. Will they revert to their former state, and if they do, will epinephrine again benefit them? Also, what changes in living habits might avert these climatic effects? What part does this functional disturbance play in accounting for the general changes in people of all races so characteristic of life in the tropics and the Orient? It will take time to answer these questions, and, since I am returning to America in June of this year, the present report is submitted in the hope that it will aid in the final solution of the larger problem of climatic effect on man. This is not a problem only of the tropics and the Orient, however, as it is likely to present itself anywhere in subtropical lands where heat and humidity present coincidental and sustained maxima. With the present intensive commercial development of such countries, it becomes important that a survey of them be made with this climatic effect in mind.

The prompt and beneficial action of epinephrine in almost all the cases in which it was tried throws important light on the nature of the disturbance. This in itself is not, of course, direct proof that there is suprarenal insufficiency. It is strongly suggestive that such is the case, however, and becomes still more important when considered in the light of the type of disturbances present and the autopsy observations in the second case presented.

In most instances the epinephrine was given orally according to the following prescription:

	Gm. or Cc.
℞ Solution of epinephrine hydrochloride	20
Dextrose	30
Syrup of citric acid	10
Distilled water—sufficient to make	100

5 cc. to be given orally half hour before meals.

The use of dextrose is based on the observations in Germany [9] that it prevents oxidation of the epinephrine. In a few instances, epinephrine

9. Unna, P. G.: Dermat. Wchnschr. **75**:685, 1922; abstr. of Ars. Medici, 1922, vol. 12, p. 406, which contained a review of "Lehrbuch der Organotherapie" by Wagner von Jaureg and Gustav Bayer.

solution (1:1,000) was given sublingually in from 0.5 to 1 cc. dosage, and in two cases it was given subcutaneously. Whether given according to the foregoing prescription or sublingually, the effect seemed just as satisfactory as when it was injected; in fact, the oral administration seemed preferable in that it did not cause systemic cardiovascular or metabolic disturbances of any kind. In two instances of hypersusceptibility to epinephrine, there was rather severe gastric pain from ten to twenty minutes after the dose of 5 cc. had been swallowed. The pain lasted about twenty minutes, and was not followed by further unpleasantness. Smaller doses of 3 cc. were well tolerated by these two patients.

Many physicians doubt the effectiveness of epinephrine given orally, but the belief that such doubt is unfounded is growing among critical observers. The principal point to bear in mind is that the effects of the drug given orally may be different from those following its use by injection. By the latter method of administration, one may cause a considerable rise in blood pressure, a quickening of the pulse rate, and a marked relaxation of normal or spastic smooth muscle in other parts of the body. The blood sugar and consumption of oxygen are increased, and blood clotting is quickened. Great prostration may be produced by a slight overdosage. When given orally, on the other hand, none of these reactions occur in normal animals or man. In case too large a dose is given, there may be gastric pain for from ten to twenty minutes, presumably from an intense vasocontrictive action on the gastric mucosa, but one sees none of the changes in the body that follow injection. These facts were verified by Menninger,[10] who used large doses (from 2 to 6 mg.) mainly on patients with hyperthyroidism, who are usually most sensitive to epinephrine. He fell into the common error, however, of stating that the drug is unsatisfactory for oral use, because it does not produce any effects in people with good suprarenal function. He did not try it in a single case in which symptoms of suprarenal insufficiency were exhibited and in which effects would be more likely to be demonstrated. A normal person taking epinephrine orally according to the prescription given is not aware of any effects. Only in patients exhibiting a hypermotility or spasticity of the smooth musculature of the bronchioles, gastro-intestinal or genito-urinary tract are prompt effects obtained. In these cases, the inhibitory influence of the drug goes only so far as to reduce the motor function to a normal level. Thus in either severe spastic constipation or watery diarrhea, the oral administration of epinephrine causes only a return to normal function.

It was this inability to demonstrate such effects from epinephrine on laboratory animals that led Stewart [11] to attack the many clinical observa-

10. Menninger, W. C.: Oral Administration of Epinephrine, Arch. Int. Med. **40**:701 (Nov.) 1927.

11. Stewart, G. N.: Endocrinology **5**:283, 1921.

tions on suprarenal insufficiency. The reply of Sajous [12] to Stewart emphasizes the point that failure to demonstrate a condition or result in normal animals does not necessarily vitiate observations made on disease conditions in man. That suprarenal insufficiency as a clinical entity does exist is practically beyond doubt. French writers [13] recognized the condition as existing to some extent among troops during trench warfare, and obtained good results by the use of epinephrine. Many of the symptoms described by them were similar to those seen in my patients, except that diarrhea was not mentioned as a frequent occurrence. The point I wish particularly to stress is that this interference with suprarenal function may be widespread in its occurrence, perhaps to be classed as a major cause of disease rather than as a rarity. Future studies may show that this effect of tropical heat is an important factor in determining the physical and mental characteristics of races subjected to such climatic influences.

The conception of suprarenal function elaborated by Cannon [14] that these glands fulfil emergency needs by quickly secreting epinephrine to stimulate the body would lead one to think that they would benefit in time of hot humid weather by obtaining a complete rest. Such, however, does not seem to be the case. If the suppression is sufficient to produce symptoms, the recovery of function seems to be slow, so that patients may show increasing signs of insufficiency as the colder weather places a greater burden on the glands.

A few months ago, I reported [15] the occurrence of fatal reactions from insulin among Chinese patients with dosages as low as 4 units. In view of these more recent observations of suprarenal insufficiency, it seems probable that this may supply an explanation of the insulin reactions. Britton and Geiling [16] found that the operation of medullectomy, or the removal of the right suprarenal and denervation of the left, caused animals to be susceptible to insulin, convulsions coming on after as little as one tenth of the normally harmless dose. An injection of epinephrine protected these animals against reaction to insulin. Voigtlin and Dunn [17] found the toxicity of insulin for white rats to be increased

12. Sajous, E. de M.: Endocrinology **6**:198, 1922.

13. Loeper, M., Bettzard and Wagner: Bull. et mém. Soc. méd. de hôp. de Paris **41**:903, 1917. Ramond, F., and Francois, R.: Ibid. **41**:1001, 1917. Josué, O.: Paris méd. **19**:13, 1917. Carles, J.: J. de méd. de Bordeaux **89**:185, 1918; abstr. J. A. M. A. **71**:858 (Sept. 7) 1918.

14. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton & Company, 1918.

15. Mills, C. A.: China M. J. **41**:914, 1927.

16. Britton, S. W., and Geiling, E. M. K.: Am. J. Physiol. **81**:467, 1927.

17. Voigtlin, C., and Dunn, E. R.: U. S. Pub. Health Service, Pub. Health Rep., 1923, p. 1747.

as the temperature under which the rats were kept was raised. These facts should serve as a warning against the unguarded use of insulin in the tropics or Orient or the free use of it such as one sees in American clinics.

Many textbooks on physiology state that sympathetic impulses cause constriction of the gastro-intestinal sphincters, with relaxation of the intervening segments of intestine. Shipley and Blackfan,[18] however, showed that surviving strips of the musculature of the pyloris of newborn pigs and human infants are regularly relaxed by solutions of epinephrine in vitro. My results on patients also show a prompt and efficient relaxation of the various sphincters after the use of epinephrine orally. The conclusion seems justified that epinephrine in physiologic amounts serves only to cause relaxation throughout the gastro-intestinal tract. I have not found any reference to the use of epinephrine in the treatment of infants with pylorospasm. A trial of such usage would seem indicated.

As to the mechanism of the action of epinephrine in dysmenorrhea and menorrhagia, nothing definite is known.

SUMMARY AND CONCLUSIONS

1. A functional disturbance common in the tropics and Orient is described and illustrated by a report of forty cases seen during the last few months. The principal features of the disturbance are: (*a*) hypermotility of the gastro-intestinal tract, with frequent occurrence of cardiospasm, pylorospasm and ileocecal or sigmoid spasm; (*b*) these motor disturbances may lead to nausea, vomiting, epigastric or abdominal pain and either diarrhea or constipation. The pain and other symptoms may simulate chronic appendicitis, peptic ulcer or tuberculous enteritis; and (*c*) there is also usually present gastric hypochlorhydria or achlorhydria, marked vascular hypotension and moderate anemia. Hypoglycemia with high tolerance for dextrose, weakness and loss in weight, urticaria, edema, pigmentation of the skin and menorrhagia also were observed.

2. Foreigners are more susceptible to this trouble than the natives.

3. It seems to be definitely related to the coincidental peaks of humidity and heat, when cooling of the body becomes difficult. In some of the foreigners, the onset of trouble was clearly associated with their first contact with the intense humid heat, while in many others the onset followed their first summer in China.

4. Relief of the symptoms by the oral administration of epinephrine was usually immediate and complete.

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18. Shipley, P. G., and Blackfan, K. D.: Bull. Johns Hopkins Hosp. **33**:159, 1922.

5. Autopsy in one case did not show anything to account for the severe condition except changes in the suprarenals characteristic of those seen in animals subjected to moist heat.

6. The conclusion seems justified that suprarenal insufficiency is responsible for the clinical picture presented, and that this represents a distinct disease entity just as truly as does hypothyroidism or hyperthyroidism.

7. Subsidiary conclusions to be drawn from this report are: (*a*) diagnosis of tuberculous enteritis, peptic ulcer or chronic appendicitis should be made with due caution to rule out all purely functional disturbances; (*b*) as a treatment for spastic constipation, the oral administration of epinephrine seems effective and often curative; and (*c*) many patients with so-called sprue are possibly suffering from suprarenal insufficiency.

ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS

III. THE ABSORPTION OF UNALTERED EGG PROTEIN IN ADULTS *

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The technic adopted for studying the absorption of unaltered egg protein was similar to that employed in the previous study of fish absorption.[1] Egg was excluded from the subject's diet on the day of passive local sensitization, which was accomplished by the intradermal injection of about 0.05 cc. of the K egg serum. The egg meal was usually taken the following morning on an empty stomach. The reaction times were recorded in the same manner as in the previous studies.

The serums used in these studies, K_4, K_5 and K_6, were taken on three different occasions from the same egg-sensitive patient, whose history has already been described in the first communication.[2] While samples K_5 and K_6 were slightly weaker in reagin content than K_4, they were all used interchangeably in these studies, as the differences between them were not considered sufficiently great to alter the results materially. Most of the tests were done with K_4. The 1 : 10 dilution was employed for reasons already noted in the previous communication.

The protein meal in the earlier tests usually consisted of one raw egg. In later studies, when it was found that the serum did not contain reagins for the egg yolk, only the egg white was used. The egg was swallowed unaltered or beaten up in a small amount of milk. The use of diluents or the amount employed did not seem materially to alter the results. The largest amount of diluent employed was from 4 to 6 ounces (118.4 to 178 cc.) (an eggnog or egg malted milk). The usual amount was 1 or 2 ounces (30 or 59 cc.) of milk. Whenever possible, the diluent was avoided.

The subjects selected for study in this series were almost all patients in hospitals. While some patients with gastro-intestinal diseases were included, most of the subjects were free from such disturbances. The diagnoses in each case are noted in table 1. With only one or two excep-

* From the Jewish Hospital of Brooklyn, and from the Department of Bacteriology and Immunology, Division of Immunology, Cornell University Medical College and the New York Hospital.

1. Brunner, M., and Walzer, M.: Arch. Int. Med. **42**:172 (Aug.) 1928.

2. Walzer, M.: J. Immunol. **14**:143, 1927.

tions, these patients were tested when free from fever. Members of both sexes were included in the series. All but two of the subjects were adults. The youngest studied was 12 years of age.

RESULTS OF TESTS

The reaction times and results of the tests are tabulated in table 1. When the exact reaction time was not obtained or the reading was not

TABLE 1.—*Data of Tests in Each Case*

Case No.	Date	Age	Sex	Diagnosis	Sensitizing Serum	Protein Meal	Reaction Time in Minutes: Undiluted Serum	Reaction Time in Minutes: Dilution 1 : 10
1	2/15/26	60	M	Gastric carcinoma.....	K_4	Egg in 1 oz. milk	..	45
2	2/15/26	37	M	Gonorrheal arthritis....	K_4	Egg in 1 oz. milk	..	80
3	2/15/23	48	M	Pneumonia convalescent	K_4	Egg in 1 oz. milk	..	50
4	2/15/26	51	M	Cardionephritic syphilis.	K_4	Egg in 1 oz. milk	..	45
5	2/15/26	38	M	Cardiac decomposition.	K_4	Egg in 1 oz. milk	..	50
6	2/15/26	30	M	Duodenal ulcer.....	K_4	Egg in 1 oz. milk	..	0
7	2/15/26	17	M	Ulcerative colitis.....	K_4	Egg in 1 oz. milk	..	43
8	2/15/26	30	M	Pyelonephritis	K_4	Egg in 2 oz. milk	..	60
9	2/15/26	34	F	Hypertension	K_4	Egg in 2 oz. milk	..	45
10	4/14/26	36	F	Enterocolitis	K_4	One white of egg	..	26
11	4/14/26	51	M	Gastric carcinoma.....	K_4	One white of egg	..	10
12	4/14/26	44	M	Gastric ulcer.....	K_4	One white of egg	..	45
13	4/14/26	45	M	Suppuration of kidney	K_4	One white of egg	..	130
14	4/14/26	50	M	Osteosarcoma of rib....	K_4	One white of egg	..	0
15	5/27/26	12	M	Endocarditis	K_4	One white of egg	..	100
16	5/27/26	32	M	Cerebrospinal syphilis..	K_4	One white of egg	..	0
17	5/27/26	40	F	Cholecystitis	K_4	One white of egg	..	50
18	6/ 7/26	28	M	Acute rheumatic fever..	K_4	One white of egg	..	91
19	6/ 7/26	58	M	Hepatic cirrhosis.....	K_4	One white of egg	..	45
20	6/ 7/26	23	F	Psychasthenia	K_4	One white of egg	..	0
21	6/ 7/26	25	F	Hyperthyroidism, cholecystitis	K_4	One white of egg	..	30
22	6/ 7/26	39	F	Polycythemia	K_4	One white of egg	..	90
23	6/ 7/26	50	F	Hypertension and cholecystitis	K_4	One white of egg	..	30
24	7/ 2/26	49	M	Asthma, achlorhydria..	K_5	One egg	..	30
25	8/21/26	22	F	Asthma	K_5	White of egg in 1 oz. of milk	50	55
26	9/ 3/25	55	F	Gastric carcinoma.....	K_4	Egg in 4 oz. milk	..	..
27	4/17/26	37	M	Hookworm	K_4	2 eggs	..	..
28	8/25/25	Adult	M	Lichen planus.....	K_4	One egg	..	..
29	8/25/25	Adult	M	Acrodermatitis atrophicans	K_4	One egg	..	..
30	1/27/26	Adult	M	Acrodermatitis atrophicans	K_4	One egg	..	..
31	10/20/25	Adult	M	Psoriasis	K_4	One egg	..	..
32		32	M	Normal	$K_{4,5,6}$	One egg	45	48*
33		44	M	Normal	$K_{4,5,6}$	One egg	30	30*
34	6/10/26	38	F	Normal	K_6	One egg	33	..

* The average of several tests

considered trustworthy, the positive reaction was designated by a + sign; 0 designated a faliure to react. The results of the entire series are summarized in table 2.

It will be noted that the results in this series are similar to those obtained in the studies with fish proteins not only in the total percentage of positive reactions with each dilution but in the relative percentages of positive reactions with the various dilutions. In both series, the undiluted serum gives a slightly higher percentage of positive reactions than the 1 : 10 dilution.

Of the five patients who failed to react, four were not tested with the undiluted serum. Had it been possible to do this, it is probable that the percentage of cases demonstrating the reaction would have been even higher than has already been noted. Only two of the five patients giving negative reactions were tested by local intradermal injection of an egg solution into the serum site to determine whether they had been successfully sensitized. Both gave marked local reactions, thus ruling out failure to accept passive local sensitization as an explanation for the negative results of the test. In view of the consistently positive reactions when patients were tested locally in the studies with fish proteins, the routine local testing of patients giving negative reactions in the present series was not strictly adhered to. Failure to accept local passive sensitization with the K egg serums seemed highly improbable, as those types of cases in which this was apt to occur were not included in the present series (see the first paper of this series [2]).

TABLE 2.—*Summary of Results of Tests*

	Undiluted	1:10 Dilution
Number of patients tested with each dilution	10	28
Number of patients demonstrating absorption phenomenon with each dilution	9	23
Percentage of patients demonstrating the phenomenon with each dilution	90	82.1
Total number of patients in series	34	
Total number of patients failing to manifest the phenomenon	5	
Percentage of patients demonstrating the absorption phenomenon	85.3	

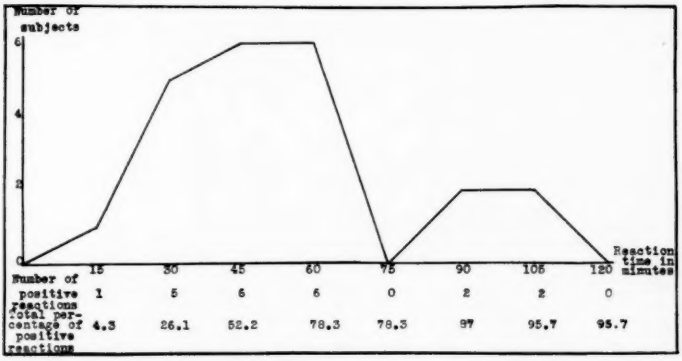
REACTION (ABSORPTION) TIME

The reaction times in the patients in this series were graphically represented, as shown in the accompanying illustration. Only the results with the 1 : 10 dilution were thus tabulated, as the patients tested with the undiluted serums were too few in number to be of service in this respect.

Of the twenty-three positive reactions occurring with the 1 : 10 reaction, only one (4.3 per cent) occurred in the first fifteen minutes. This is in sharp contrast to the reaction time in the patients tested with fish proteins, in which 32 per cent occurred within this period. In the second, third and fourth fifteen minute periods, there were five, six and six reactions, respectively. Therefore, eighteen of the twenty-three reactions, or 78.3 per cent, occurred within the first hour. In the patients tested with fish proteins, 86.3 per cent of the reactions had occurred within half that time, thus indicating a definitely slower absorption of unaltered egg protein than of fish. The average reaction time in the series tested with egg protein was about fifty-six minutes. That of the series tested with fish serum was about twenty minutes.

FACTORS AFFECTING REACTION TIME

The same factors affecting the absorption in the studies of the patients tested with fish were found to apply in the series tested with egg as well. The administration of other food before the ingestion of egg definitely prolonged the reaction time. This was well illustrated in patients 4 and 5, who were first given the yolk of eggs. As reagins for egg yolk are not present in the K egg serum, reactions did not result. After ninety minutes, a whole egg in 1 ounce of milk was given to each. In this instance, the patient in case 4, whose normal reaction time was forty-five minutes, reacted in ninety-three minutes. The reaction time in case 5 was similarly increased from fifty to ninety-five minutes. The local reactions in both were considerably less active than when tested under routine circumstances, that is, when the egg white was taken on a fasting stomach.


Number of subjects
6
4
2
0
Reaction time in minutes
Number of positive reactions
Total percentage of positive reactions
15 30 45 60 75 90 105 120
1 5 6 6 0 2 2 0
4.3 26.1 52.2 78.3 78.3 87 95.7 95.7

Graph representing reaction (absorption) times of the twenty-three patients sensitized with a 1:10 dilution of serum who demonstrated the absorption of unaltered egg protein.

It seemed of interest to determine the effect of peptone taken before the protein meal on the degree and rapidity of the reaction. The work of Pagniez and Vallery-Radot [3] and other French writers suggests the use of 0.5 Gm. of peptone given from one-half to one hour before meals as a preventive in those cases of allergy due to food sensitivities. As these conditions are due to absorption of protein in its unaltered state, it seemed important to determine, if possible, the effect of peptone on the phenomenon. Three subjects whose normal reaction times were known were therefore given capsules containing 0.5 Gm. of Witte's peptone siccum from forty-five to sixty minutes preceding the egg protein

3. Pagniez, P., and Vallery-Radot, P.: Presse méd. **24**:529, 1916.

meal. As a result of this, in case 4, the reaction time was increased from forty-five to ninety-three minutes; in case 3, it was reduced from fifty to twenty minutes; in case 17, it remained unaffected. The use of peptone, moreover, seemed not to have a consistent effect on the degree or severity of the local reaction. There did not seem to be any evidence, therefore, that peptone administered in the manner described influenced the absorption of unaltered protein in any definite manner.

ABSORPTION OF UNALTERED PROTEIN FROM THE RECTUM

Nine of the cases tested in table 1 were studied for the purpose of determining whether absorption of unaltered protein from the rectum could be detected by the same technic as that employed for proteins administered orally.

TABLE 3.—*Results of Rectal Administration of Protein*

Case	Date	Age	Sex	Diagnosis	Sensitizing Serum	Preliminary Preparations	Protein Rectally Administered	Reaction Time in Minutes: Undiluted Serum	Dilution 1:5	Dilution 1:10	Oral Reaction Time
7	2/15/26	17	M	Ulcerative colitis	K4	.....	1 egg white in 2 oz. milk	..	..	7	43
	4/17/26	..	..	.....	K4	.....	1 egg white in 2 oz. milk	..	..	26	..
10	4/17/26	36	F	Enterocolitis	K4	Test preceded by enema	1 egg white in 2 oz. water	..	..	65	26
12	4/17/26	44	M	Gastric ulcer	K4	Test preceded by enema	1 egg white in 2 oz. water	..	..	±*	45
13	4/17/26	45	M	Suppuration of kidney	K4	Test preceded by enema	1 egg white in 2 oz. water	..	0	..	130
16	6/10/26	32	M	Cerebrospinal syphilis	K4	Test preceded by enema	1 egg white in 2 oz. water	..	0	..	0
23	6/10/26	50	F	Hypertension, cholecystitis	K4	Test preceded by enema	1 egg white in 2 oz. water	..	±*	..	30
22	6/10/26	39	F	Polycythemia	K4	Test preceded by enema	1 egg white in 2 oz. water	..	54	..	90
25	8/23/26	22	F	Asthma	K5	Test preceded by enema	1 egg white in 2 oz. water	75	..	125	55
27	4/20/26	30	M	Hookworm	K4	Test preceded by enema	2 eggs in 2 oz. of water	0	..	0	0

* ± indicates a slight reaction with slight erythema and slight pruritus without formation of wheals.

Preparation of the patient and sensitization were accomplished as before. The egg was administered by rectal tube, either unaltered or diluted in water or milk. In some cases, an enema was given before the rectal feedings, to clean out the lower bowel. The results in each case are noted in table 3.

The patients in cases 16 and 27, who failed to exhibit a positive reaction following oral administration of the egg, gave negative results with the rectal feeding as well. (In case 27, the patient has already been pointed out in the previous communication as the one who failed to demonstrate the reaction to both fish and egg when given orally, rectally or enterally.) The patient in case 13, who showed a delayed reaction time after oral administration, failed entirely to exhibit the phenomenon following rectal administration. The patient in case 7, who had large

ulcerative areas in the sigmoid and colon, exhibited a much more rapid and active reaction with the rectal than with the oral administration. The first test, made while the ulcerative process was acute, resulted in a marked positive reaction in seven minutes. The oral reaction time was forty-three minutes. With the inflammatory process subsiding, the rectal test was repeated two months later, the reaction this time appearing in twenty-six minutes. Case 22 was another in which the reaction time after rectal administration was more rapid than that by mouth. In cases 12 and 23, the local reactions following rectal administration were extremely mild, consisting of erythema and slight itch. In case 12, they were decidedly tardy in appearance, coming on as late as three and seven hours, respectively, in two instances. In cases 10 and 25, the reaction times after rectal administration were slightly longer than the oral.

Judging from the foregoing results, it would seem that absorption of unaltered protein generally occurs to a less degree from the rectum than from the upper digestive tract. It is also apparent that failure to demonstrate the phenomenon following oral administration of the protein under routine conditions is not necessarily to be considered as the result of some local factors in the upper digestive tract, such as hyperacidity and delayed emptying of the stomach. For it is noted that those showing delayed or absent reactions following oral ingestion usually do not show absorption from the rectum. The trait is therefore a constitutional rather than a local one or, if it involves the intestine itself, affects the entire alimentary system. The foregoing experiments, however, demonstrate beyond a doubt that rectal absorption of unaltered protein does occur in detectable quantities in most persons.

SUMMARY

1. The absorption of detectable amounts of unaltered egg protein from the digestive tract was noted in 85.3 per cent of thirty-four subjects tested and may therefore be considered a normal phenomenon.

2. The unaltered egg protein was detected in the blood stream in the first fifteen minutes in only one case, or 4.3 per cent. Twenty-six and one-tenth per cent of the reactions occurred within the first half hour, and 78 per cent within the first hour.

3. The same factors affecting the absorption time of fish protein affected that of egg protein as well.

4. Absorption of unaltered egg protein from the rectum was demonstrated in most cases in which it had occurred after oral administration. Patients who showed diminished or negative absorption after oral administration usually failed in the rectal test. This indicated that negative reactions usually could be attributed to a constitutional rather than a purely local cause.

5. Absorption from the rectum was usually somewhat slower and less pronounced than that from the upper enteral canal.

PERITONITIS

IV. PRODUCTION OF ACTIVE IMMUNITY AGAINST THE FATAL OUTCOME OF EXPERIMENTAL FECAL PERITONITIS *

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In a previous communication,[1] it was shown that active immunity can be produced in dogs against a fatal outcome following "colon bacillus-gum tragacanth" peritonitis. Since one of the more common causes of peritoneal infection is soiling of the peritoneum by intestinal contents, this investigation was undertaken to determine whether active immunity can also be developed against a fatal outcome in this type of peritonitis. Since colon bacillus is found with and without other organisms in a high percentage of cases of peritonitis due to rupture of the appendix or perforation of intestines, it was determined to investigate the capacity of the colon bacillus alone to produce active immunity against the fatal outcome of fecal peritonitis.

EXPERIMENTAL METHOD AND EXPERIMENTS

Method.—In preliminary experiments, it was found that the intraperitoneal injection into a dog of a saline suspension of 5 Gm. of solid feces from the lower portion of the small intestine or from the large intestine of another dog invariably produced severe serohemorrhagic and fibrinopurulent peritonitis, which always proved fatal. This amount was therefore adopted in the following experiments as the standard for the production of fatal fecal peritonitis.

In order to produce immunity, colon bacilli were injected intraperitoneally into dogs by the following method. Living organisms were used for purposes of immunization in one series of animals and in another, dead organisms were used. The dead colon bacilli were produced by heating the saline suspension of the living organisms at 58 C. for one hour. Cultures made of the heated suspensions proved sterile.

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* From the Division of Laboratories and Research, Toledo Hospital, Toledo, Ohio, and the Department of Pathology, School of Medicine, Western Reserve University, Cleveland.

1. Goldblatt, H., and Steinberg, B.: Peritonitis: III. Active Immunization Against Experimental B. Coli Peritonitis, Arch. Int. Med. **41**:42 (Jan.) 1928.

Four intraperitoneal injections were given, the interval between successive doses being four days. The initial injection consisted of the saline washings of one agar slant of the organisms and the remaining three injections of two, three and four agar slants, respectively. This is exactly the same procedure that was employed in a previous investigation.[1] On the fifteenth day after the last injection, the presence of immunity was tested by the intraperitoneal injection of 5 Gm. of solid feces suspended in 15 cc. of 0.9 per cent sodium chloride solution. As a control of the experiment, a similar injection of feces was given at the same time to nonimmunized normal dogs. Smears of the feces used showed abundant and varied bacteria which included relatively many large and small gram-negative bacilli, gram-positive diplococci and a few large gram-positive bacilli. Colon bacilli were identified by cultural methods, but no attempt was made to identify all the other organisms.

Immunization with Living Colon Bacilli.—Eleven dogs were immunized with living colon bacilli by the foregoing method; group A (six dogs) at one time, and group B (five dogs) at another time. On the fifteenth day after the last immunizing injection, the animals were given the intraperitoneal injection of fecal material. For from twelve to thirty-six hours they showed varying degrees of malaise and vomited frequently. Of the six animals in group A, all survived; of the five in group B, four survived, and one died in forty-eight hours. Thus, of the total of eleven dogs, ten survived. One died in forty-eight hours, and autopsy revealed a severe serous and fibrinopurulent peritonitis.

Four days after the fecal injection, one of the animals of group A, clinically completely recovered, was killed, and autopsy showed the presence of some free pus in the peritoneal cavity with some fibrinopurulent exudate on the visceral and parietal peritoneum. One month after the injection of the feces, another dog of group A, at the time in excellent condition, was killed; autopsy did not show any gross abnormalities of the peritoneum. Six weeks after the injection of feces, one dog of group B was killed, and autopsy showed only a few fibrous adhesions between the upper surface of the liver and the under surface of the diaphragm. The remainder are still alive several months after the injection of the feces.

Immunization with Dead Colon Bacilli.—Eight dogs were immunized with dead colon bacilli by the method described; group A (six dogs) at one time, and group B (two dogs) at another time. Fourteen days after the last immunizing injection, the animals were given an intraperitoneal injection of the fecal material. In this series, the fecal injection was made in groups A and B on the same days and with the same fecal material used for groups A and B of the series immunized with living colon bacilli. Of the six dogs in group A, two survived, and of the two

in group B, one survived. Of the total of eight dogs, therefore, three survived and were still living several months later. The remaining five dogs died in from twenty-two to sixty hours following the fecal injection. All of the dogs were ill. Those that survived had severe malaise, and vomited for from twelve to twenty-four hours. For the next two days the animals refused solid food and were somewhat lethargic, but from that time on, the return to normal was rapid and complete. The dogs that did not recover continued to vomit, were finally prostrated and were comatose for several hours before death. Autopsy showed severe serohemorrhagic and fibrinopurulent peritonitis.

A. Injection of Fecal Material into Nonimmunized Normal Dogs.—Fifteen normal dogs (six in group A, and nine in group B), were given the intraperitoneal injection of feces on the same day and with the same

Active Immunization Against a Fatal Outcome of Experimental Fecal Peritonitis in Dogs

Number of Dogs	Immunizing Agent	Outcome
11 (group A — 5) (group B — 6)	Living colon bacilli	10 survived (group A — 4) (group B — 6) 1 died in 48 hours (group A)
8 (group A — 6) (group B — 2)	Dead colon bacilli (killed by heat)	3 survived (group A — 2) (group B — 1) 5 died in from 22 to 60 hours (group A — 4) (group B — 1)
15 (group A — 6) (group B — 9)	None	15 died in from 12 to 24 hours
3*	None	3 survived

* The fecal material used for this group was sterilized by heat.

material used for groups A and B of the series immunized by living and dead bacilli. All of the dogs died in from twelve to twenty-four hours. Autopsy showed severe hemorrhagic serous and fibrinopurulent peritonitis.

Smears of the peritoneal exudate of these dogs showed similar organisms to those seen in the feces used for injection; namely, small and large gram-negative bacilli, gram-positive cocci and large gram-positive bacilli. Smears of the peritoneal exudate from the immunized dogs that died showed similar organisms. Similar organisms were also recovered in cultures, but no attempt was made to identify any except colon bacilli which were present in abundance.

B. Injection of Heated Fecal Material into Nonimmunized Normal Dogs.—To test the effect of the feces, independent of living organisms, three animals were given intraperitoneal injections with the standard amount of saline suspension of fecal material which had been heated for one hour at 60 C. This was a portion of the feces used for groups B.

Cultures of the heated feces proved sterile. The three animals survived. One was killed seventy-two hours after the fecal injection, and autopsy did not reveal any gross peritoneal lesion.

COMMENT

It is apparent from the results of these experiments that it is possible to prevent the fatal outcome of fecal peritonitis in dogs by active immunization with living colon bacilli. In this communication, no explanation is offered for this phenomenon. Whether death in fecal peritonitis is entirely due to the action of the colon bacillus and the active immunization with these organisms results in the production of specific antibodies or protective cellular reaction, or whether the immunity produced by *Bacillus coli* is nonspecific, and of cellular or humoral nature, or both, remains an open question.

The experiments in which colon bacilli, killed by heat, were used to produce immunity showed protection in a small percentage of the animals. This would indicate that dead organisms might be employed for the production of active immunity against a fatal outcome in fecal peritonitis, but that heat destroys a great part of the antigenic power of the organisms. Other methods of killing the bacteria are being employed for the further investigation of active immunization with dead colon bacilli against the fatal outcome of fecal peritonitis.

SUMMARY AND CONCLUSIONS

1. The intraperitoneal injection into fifteen normal dogs of 5 Gm. of solid feces suspended in 15 cc. of physiologic sodium chloride solution invariably resulted in the production of severe serous and fibrinopurulent peritonitis which always proved fatal.

2. Active intraperitoneal immunization with "living" colon bacilli resulted in the survival of ten of eleven dogs after an intraperitoneal injection of feces.

3. Active intraperitoneal immunization with "dead" colon bacilli, killed by heat, resulted in the survival of three of eight animals after an intraperitoneal injection of feces. Killing by heat greatly diminishes the antigenic power of colon bacilli.

4. Heated feces did not produce peritonitis, and the three dogs into which this substance was injected survived. The bacteria of fresh feces are therefore necessary for the production of peritonitis and the fatal outcome.

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RELATIVE LYMPHOCYTOSIS IN HYPERTHYROIDISM *

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In 1908, Kocher [1] pointed out that the differential formula in cases in which patients were suffering from exophthalmic goiter might be abnormal, showing a preponderance of lymphocytic elements. He thought that this relative lymphocytosis represented an index of the severity of the disease. In a recent communication,[2] I reported on the production of a relative mononucleosis in normal animals, occurring after a period of excitement lasting from ten to fifteen minutes. This emotional relative mononucleosis was evidently connected with sympathetic activation of lymphoid structures, particularly the spleen, for it was shown that removal of the sympathetic strands in an animal, splenectomy, or merely denervation of the spleen could inhibit this physiologic increase in the relative mononuclear counts after excitement.

The present clinical study was undertaken in order to ascertain the incidence of relative lymphocytosis in cases of hyperthyroidism, and also the character of the differential formula in patients who have recovered or who have a normal basal metabolism after subtotal or partial thyroidectomy has been performed. Through such a study it was thought that a correlation might be made between the experimental observations already mentioned on the production of a relative emotional mononucleosis and the clinical symptoms in exophthalmic goiter in which the sympathetic system is presumably overstimulated.

INCIDENCE

One hundred cases of hyperthyroidism were collected from the records of the Peter Bent Brigham Hospital. In sixty-seven cases the patients showed a definite relative lymphocytosis of 30 per cent or more (table). Fifty-six per cent of the 100 patients in this series had signs of exophthalmos. Eighty per cent of this group, namely, those having hyperthyroidism and exophthalmos, showed a definite relative lymphocytosis. In the group of patients having hyperthyroidism as revealed by the clinical picture and the basal metabolism but without signs of exophthalmos, only 50 per cent showed a definite relative lymphocytosis (table). It would seem as if a relative lymphocytosis is somewhat more

* From the Medical Service of the Peter Bent Brigham Hospital.

1. Kocher, T.: Blutuntersuchungen bei Morbus Basedowii, Arch. f. klin. Chir. **87**:131, 1908.

2. Menkin, V.: Emotional Relative Mononucleosis, Am. J. Physiol. **85**:489, 1928.

Percentage of Lymphocytes in One Hundred Cases of Hyperthyroidism

Case No.	Hyperthyroidism With Exophthalmos, Percentage of Lymphocytes
24890	43
——	52
20351	40
20751	42
20792	34
21069	32
21080	33
22017	35
22256	45
20315	46
21626	44
22560	33
20022	48
18974	22
18955	28
18975	46
23794	24
22275	18
18893	12
29848	30
25017	51
25073	43
25035	49
25367	33
25424	34
29051	20 (slight)
26080	46
26151	45
26342	44
22063	37 (slight)
238-2	42 (lid lag only)
22781	31
23068	42
23524	27
23576	39
23469	48
23937	34
23871	52
24012	38
24184	26
24377	52
23815	57
29729	23 (slight)
29080	43 (slight)
29034	20
28896	28
E. B.	41
El. G.	48
C. B.	47
E. S.	42 (slight)
D. R.	45
E. H.	42 (lid lag only)
E. R.	52
W. L.	51
B.	32
R. M.	39 (lid lag only)
Average	38%

Case No.	Hyperthyroidism Without Exophthalmos, Percentage of Lymphocytes
18932	31
20364	60
20632	32
20641	31
20758	31
21243	32
22302	43
22331	33
22369	23
20270	21
19829	29
21174	26
22150	19
18872	15
29946	30
29860	26
30447	18
30610	33
30585	41
30135	30
29499	20
30086	35
25092	25
24958	40
25360	52
25769	25
26106	28
25936	26
27036	27
27019	18
23042	29
23260	32
23588	48
24104	20
23970	54
29606	20
29489	40
29499	20
29792	30
25554	32
C. W.	18
E. O.	34
G. H.	20
E. G.	14
Average	30%

	Hyperthyroidism With Exophthalmos	Hyperthyroidism Without Exophthalmos
Total number of cases	56	44
Number of cases with relative lymphocytosis (30 per cent or more)	45	22
Percentage with relative lymphocytosis	80	50

prone to occur in cases of hyperthyroidism exhibiting also exophthalmos than in cases having hyperthyroidism, but without abnormal eye signs. This fact is suggestive in view of a possible generalized sympathetic activation of lymphoid structures in cases in which exophthalmos is superimposed on the hyperthyroidism.

DIFFERENTIAL FORMULA AFTER THYROIDECTOMY

As pointed out in the foregoing, relative lymphocytosis is more apt to be found in patients having definite exophthalmos in addition to other signs of hyperthyroidism. Will this abnormal blood picture disappear after subtotal thyroidectomy, or is the condition associated with a concomitant hyperplasia of lymphoid structures bearing no direct relationship to the thyroid gland? The present study was undertaken in an attempt to answer this question. Ten patients were followed up with the accompanying results in each case.

REPORT OF CASES

CASE 1.—E. B., a woman, aged 32, entered the Peter Bent Brigham Medical Service in November, 1923. The basal metabolism was + 57. Exophthalmos was not present. The differential count showed: polymorphonuclears, 68 per cent; lymphocytes, 26 per cent; eosinophils, 3 per cent. In December, a partial thyroidectomy was performed. In January, 1925, the patient was readmitted to the hospital with a basal metabolism of + 51, and with marked exophthalmos. The differential count revealed: polymorphonuclears, 52 per cent; lymphocytes, 41 per cent; large mononuclears, 7 per cent. Operation was again performed. In October, 1927, she reentered the hospital with a basal metabolism of + 10. The differential count was: polymorphonuclears, 80 per cent; lymphocytes, 15 per cent; large mononuclears, 4 per cent.

CASE 2.—R. B., a woman, aged 23, entered the hospital in June, 1927, with marked exophthalmos and a basal metabolism of + 39. The differential formula was: polymorphonuclears, 54 per cent; lymphocytes, 36 per cent; large mononuclears, 8 per cent; eosinophils, 1 per cent; basophils, 1 per cent. She reentered for follow-up in October, 1927. The basal metabolism was 0. The differential count revealed: polymorphonuclears, 65 per cent; lymphocytes, 26 per cent; eosinophils, 4 per cent; basophils, 2 per cent; unknown, 3 per cent.

CASE 3.—C. B., a man, aged 35, entered the hospital in September, 1924, with marked exophthalmos and a basal metabolism of + 76. The differential count showed: polymorphonuclears, 44 per cent; lymphocytes, 47 per cent; large mononuclears, 9 per cent. Partial thyroidectomy was performed. The patient was readmitted to the hospital in October, 1927; the basal metabolism was + 20; the differential count was: polymorphonuclears, 63 per cent; lymphocytes, 27 per cent; large mononuclears, 8 per cent; eosinophils, 2 per cent.

CASE 4.—E. S., a woman, aged 49, was admitted to the hospital in November, 1923, with a basal metabolism of + 12, without signs of exophthalmos. The differential count revealed: polymorphonuclears, 70 per cent; lymphocytes, 26 per cent; large mononuclears, 3 per cent; eosinophils, 1 per cent. In October, 1924, slight exophthalmos was present; the basal metabolism was + 32. The differential count showed: polymorphonuclears, 56 per cent; lymphocytes, 42 per cent; large

mononuclears, 1 per cent; eosinophils, 1 per cent. In October, 1927, the patient appeared entirely normal clinically. The differential count showed: polymorphonuclears, 69 per cent; lymphocytes, 22 per cent; large mononuclears, 8 per cent; eosinophils, 1 per cent.

CASE 5.—R. D., a woman, aged 31, entered the hospital in July, 1925, with signs of exophthalmos and a basal metabolism of + 47. The differential count revealed: polymorphonuclears, 47 per cent; lymphocytes, 45 per cent; large mononuclears, 7 per cent; eosinophils, 1 per cent. Thyroidectomy was performed. In October, 1927, the patient entered the outpatient department for follow-up. She seemed perfectly well. The differential count showed: polymorphonuclears, 60 per cent; lymphocytes, 29 per cent; large mononuclears, 7 per cent; eosinophils, 3 per cent; unknown, 1 per cent.

CASE 6.—E. R., a woman, aged 32, entered the hospital in August, 1926, with a basal metabolism of + 59, and with moderate exophthalmos. The differential count was: polymorphonuclears, 36 per cent; lymphocytes, 52 per cent; large mononuclears, 12 per cent. Subtotal thyroidectomy was performed. In November, 1927, the patient reentered for follow-up; she appeared to be well. The differential count showed: polymorphonuclears, 77 per cent; lymphocytes, 15 per cent; large mononuclears, 4 per cent.

CASE 7.—W. L., a woman, entered the hospital in December, 1924, with moderate exophthalmos. The differential count revealed: polymorphonuclears, 45 per cent; lymphocytes, 51 per cent; large mononuclears, 4 per cent. The basal metabolism was + 51. The basal metabolism test in October, 1927, was — 13, and signs of postoperative myxedema were apparent. On Nov. 15, 1927, the differential count showed: polymorphonuclears, 58 per cent; lymphocytes, 33 per cent; large mononuclears, 6 per cent; eosinophils, 3 per cent.

CASE 8.—C. W., a woman, aged 42, entered the hospital without signs of exophthalmos; the basal metabolism was + 89 on March, 1927. The differential count revealed: polymorphonuclears, 74 per cent; lymphocytes, 18 per cent; large mononuclears, 8 per cent. Subtotal thyroidectomy was performed in November, 1927; the basal metabolism was + 31; the differential count showed: polymorphonuclears, 70 per cent; lymphocytes, 22 per cent; large mononuclears, 6 per cent; eosinophils, 3 per cent.

CASE 9.—E. O., a woman, aged 35, was admitted to the hospital in December, 1926. Exophthalmos was not present; the basal metabolism was + 29. The differential count was: polymorphonuclears, 56 per cent; lymphocytes, 34 per cent; large mononuclears, 10 per cent. Thyroidectomy was performed. In November, 1927, the differential count showed: polymorphonuclears, 61 per cent; lymphocytes, 37 per cent; large mononuclears, 2 per cent.

CASE 10.—E. H., a woman, aged 54, entered the hospital in December, 1926, with a basal metabolism of + 43; exophthalmos was not present, but there was a lid lag. The differential count revealed: polymorphonuclears, 48 per cent; lymphocytes, 42 per cent; large mononuclears, 5 per cent; eosinophils, 4 per cent. On Nov. 8, 1927, the differential count showed: polymorphonuclears, 55 per cent; lymphocytes, 41 per cent; large mononuclears, 4 per cent; eosinophils, 1 per cent.

It is clear from cases 1 and 4 that a relative lymphocytosis tends to appear when exophthalmos is also present, and furthermore that this exophthalmos is apparently a later stage of the disease. Though the patient in case 7 showed a reduction in relative lymphocytosis after

thyroidectomy was performed, a high relative lymphocyte count (33 per cent) was present. Emery [3] has shown that a relative lymphocytosis is often seen in myxedema. The patient in this case showed a postoperative basal metabolism of —13; hence it is conceivable that a relative lymphocytosis of 33 per cent may perhaps be part of a postoperative myxedematous blood picture.

The patient in case 8 did not show any signs of relative lymphocytosis before operation. It is interesting to note also that there was no sign of exophthalmos in this case (table). In cases 9 and 10, the patients both showed exophthalmos and relative lymphocytosis which, however, was not relieved by operation. The patients in the remaining six cases showed exophthalmos and a relative lymphocytosis before operation. The differential formula in this group became normal after thyroidectomy was performed.

COMMENT

From this study, it seems as though a relative lymphocytosis is a frequent occurrence in hyperthyroidism, especially in cases in which a definite exophthalmos is associated with the usual signs of the disease. It is difficult to conceive of the exact mechanism which produces this relative increase in lymphocytes. Capelle [4] pointed out that in all severe cases of exophthalmic goiter there is a lymphoid hyperplasia. Marine and Lenhardt [5] consider the changes in both the thyroid and the lymphoid tissues to be the truest indexes of the severity of the disease. Definite hyperplasia of the thymus seems to be present in 75 per cent of the cases.[6] If exophthalmos is taken as an index of sympathetic overactivity resulting from thyroid intoxication, it is probable that the relative lymphocytosis of exophthalmic patients is caused by sympathetic stimulation of lymphoid structures, particularly the spleen causing a discharge of lymphocytes in the blood stream by an increase in splenic contractions. It has been shown that a similar mechanism takes place when a normal animal is excited for from ten to fifteen minutes.[2] Sympathectomy or denervation of the spleen tends to inhibit this physiologic relative mononucleosis in animals. Thyroidectomy in patients with exophthalmic goiter presumably removes a factor which stimulates the discharge of lymphoid elements into the blood stream. This would result in a sub-

3. Emery, E. S.: The Blood in Myxedema, Am. J. M. Sc. **165**:577, 1923.

4. Capelle: Die Beziehungen der Thymus zum Morbus Basedowii, Beitr. z. klin. Chir. **58**:353, 1908.

5. Marine, D., and Lenhardt, C. H.: Relation of Iodine to the Structure of Human Thyroids. Relation of Iodine and Histologic Structure to Diseases in General, to Exophthalmic Goiter, to Cretinism and Myxedema, Arch. Int. Med. **4**:440 (Nov.) 1909.

6. McCarrison, R.: The Thyroid Gland in Health and Disease, New York, William Wood & Company, 1917.

sequent restoration of the normal differential formula. Evidently patients with hyperthyroidism and without exophthalmos represent a less toxic or generalized involvement. It is difficult to account for the relative lymphocytosis in cases 9 and 10 in which exophthalmos was not present and in which operation did not relieve the condition. It is possible that in these two cases, there was not a similar mechanism of sympathetic discharge from the spleen, but rather a concomitant lymphoid hyperplasia of the thymus, and perhaps other lymphoid structures which, by their increased activity, raised the level of relative lymphocytes in the blood stream. Removal of the thyroid or of the sympathetic strands presumably would not cause any decrease of such lymphoid activity.

SUMMARY

1. Relative lymphocytosis was observed in 67 per cent of the cases of hyperthyroidism.

2. Relative lymphocytosis is more frequently seen in patients who have exophthalmos superimposed on the usual clinical signs of hyperthyroidism.

3. In patients with exophthalmos, thyroidectomy decreases the relative lymphocytosis and restores a normal differential formula.

4. It is suggested that the relative lymphocytosis in cases of exophthalmic goiter is due to sympathetic stimulation of lymphoid structures, particularly of the spleen, which causes it to contract, as evidenced by experimental work reported in a previous publication.

5. Some patients with hyperthyroidism but without signs of exophthalmos show a relative lymphocytosis apparently not relieved by thyroidectomy. The mechanism of this type of relative lymphocytosis is not clear. It is suggested that it may be caused by a concomitant hyperplasia of lymphoid structures, such as the thymus.

It gives me pleasure to express my appreciation to Dr. Henry A. Christian for suggesting this problem and for valuable assistance in carrying it out.

PERNICIOUS ANEMIA

EDEMA AND REDUCTION IN EXCRETION OF WATER *

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It is well known that patients with pernicious anemia have a more or less pronounced tendency toward edema, and that they usually have edema, especially in the later stages of the disease. Edema has always been considered a link in the clinical symptomatology of this disease, but a closer study of its pathogenesis has been limited. In most instances, edema is understood to be nephrogenetic (Makarow [1]), but it is also thought to be determined by extrarenal factors (Saltzman [2]). In both cases, the authors seem inclined to regard the anemia itself, the low hemoglobin percentage, as the determining factor.

Again, in patients with pernicious anemia, one finds a characteristic change in the excretion of water. Christian [3] and Stieglitz [4] stated that patients generally show a tendency toward fixation of the specific gravity of the urine without accompanying polyuria and with a relative increase of the nocturnal urine. Saltzman,[2] Essen and Porges [5] substantiated this opinion and at the same time found a characteristic result with the water test, namely, a retarded excretion with a tendency toward fixation of the specific gravity at a comparatively high level. This change in the excretion of water is generally understood to be nephrogenetic. Christian [3] and Stieglitz [4] expressed the opinion that it is dependent on the anatomic changes in the kidneys; Essen and Porges,[5] that it is due to deficiency of oxygen. Only Saltzman [2] spoke of the possibility of extrarenal factors being the cause of the changed excretion of water as well as the cause of the edema.

THE CLINICAL APPEARANCE OF EDEMA

In its localization, anemic edema resembles nephrotic edema to a certain extent. In both mild and severe cases, a diffuse puffiness of the face

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1. Makarow: Inaug. Diss., Jena, 1912.

2. Saltzman: Finska läk.-sällsk. Handl. **61**:1, 1919.

3. Christian: Renal Function in Anemia, Arch. Int. Med. **18**:429 (Oct.) 1916.

4. Stieglitz: Disturbances of Renal Function in Pernicious Anemia, Arch. Int. Med. **33**:58 (Jan.) 1924.

5. Essen and Porges: Wien. Arch. f. Inn. Med. **5**:195, 1922.

is noticeable, which often, to a great extent, gives patients with pernicious anemia a characteristic appearance. Edema of the lower extremities, and if the patient is in bed, edema of the lumbar region, is more or less definite. In extreme cases, marked edema of the upper extremities is found, especially in the hands. Most characteristic, however, is a peculiar diffuse retention of water in the integument and subcutaneous tissues.

In less pronounced cases, we have used the following procedure to determine "occult edema." We have placed a rubber tubing around the antibrachium and the crus and held it tight for two minutes. If there is "occult edema," a circular depression appears in the skin easily discernible to the eye and perceptible to the touch. This symptom of "occult edema" is often present in patients with pernicious anemia.

With regard to the frequency of edema in cases of pernicious anemia, 64 per cent of Cabot's [6] patients and almost 50 per cent of Schauman's [7] had edema. The frequency of finding edema, however, depends partly on what is understood as edema but mostly on the stage of the illness at which the patient was examined. We feel sure that if patients were followed until death, edema would be an almost constant symptom of the disease. A characteristic of the edema is that it appears during the relapses and disappears during the remissions. Its reappearance indicates, at a comparatively early stage, the occurrence of a new relapse.

REDUCED EXCRETION OF WATER AS DETERMINED BY THE WATER TEST

We have examined the excretion of water in thirty-five patients on whom ninety-six water tests were made. (Examinations made before knowing liver treatment.) Most of the patients were examined a number of times at different phases of the disease. One thousand grams of water were given the patient at 8 o'clock, and urine was passed at the times shown in tables 1 and 2.

A few cases will illustrate the typical change which occurs with the water test.

These tables show that the excretion of water is reduced considerably during the first four hours, and that the specific gravity is fixed near a rather high average. In these two cases albuminuria and cylindruria were not noted; the systolic blood pressure was 115 and 130, respectively; the excretion of thiosulphate, 33 and 27 per cent, respectively, and the blood urea was 27 and 44 mg. per hundred cubic centimeters,

6. Cabot, in Osler and McCrae: Modern Medicine, vol. 4, Philadelphia, Lea & Febiger, 1908.

7. Schauman, Schauman and Saltzman: Die perniziöze Anaemie, Encyklop. d. Klin. Med., Berlin, 1925.

respectively. The first patient did not show edema; the second patient had puffiness of the face, slight edema of the lumbar region and lower extremities and a positive reaction when the compression test was made on the upper and lower extremities.

In studying the results of the water test, the predominant impression is that the result of the test depends on whether the test was made during the period of relapse or during the remission. It is evident that patients first seen in a relapse often show a great reduction in the excretion of water in the beginning; when there is a remission, the excretion gradually improves and finally becomes normal.

TABLE 1.—*Data Showing Water Excretion in M. A.*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
2/1/26	35	7- 8	30		1.018
		8- 9	22		1.019
		9-10	40	Sum	1.021
		10-11	40	142	1.017
		11-12	40		1.015
		12- 6	195		1.018
		6- 7	15		1.021
		7- 6	195		1.021
		6- 7 next morning	15		1.021

TABLE 2.—*Data Showing Water Excretion in L. M*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
5/20/25	42	7- 8	15		1.022
		8- 9	21		1.021
		9-10	58	Sum	1.017
		10-11	43	151	1.019
		11-12	29		1.023
		12- 6	150		1.023
		6- 7	12		
		7- 6	240		1.024
		6- 7 next morning	20		1.016

The patient A. F. A. in table 3 is a typical example. Another example of this type is S. J., shown in table 4.

The exact reverse of this can be seen in table 5. When this patient, L. M., was discharged from the hospital, the excretion of water was normal; he had a relapse and when he returned there was a reduction in the excretion of water. These examples illustrate the fundamental principle.

In comparing the course of edema and the excretion of water, it can be said that they are usually simultaneous; that is, the edema and the reduced excretion of water are most noticeable during the severe stage of the illness. However, there is no congruity in evidence, because there can be noticeable edema at the same time that the water test

TABLE 3.—*Data Showing Water Excretion in A. F. A.*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
5/18/25	25	7- 8	102		1.019
		8- 9	80		1.019
		9-10	142	Sum	1.019
		10-11	84	350	1.019
		11-12	44		1.020
		12- 6			
		6- 7	71		1.017
		7- 6			
		6- 7 next morning	70		1.012
5/28/25	29	7- 8	21		1.019
		8- 9	68		1.019
		9-10	27	Sum	1.018
		10-11	176	441	1.011
		11-12	170		1.009
		12- 6			
		6- 7	95		1.016
		7- 6			
		6- 7 next morning	26		1.021
6/ 5/25	46	7- 8	125		1.017
		8- 9	110		1.011
		9-10	325	Sum	1.004
		10-11	330	1055	1.004
		11-12	290		1.006
		12- 6			
		6- 7	34		1.019
		7- 6			
		6- 7 next morning	78		1.024
6/29/25	60	7- 8	45		1.021
		8- 9	156		1.017
		9-10	415	Sum	1.007
		10-11	340	1161	1.008
		11-12	250		1.008
		12- 6			
		6- 7	18		1.022
		7- 6			
		6- 7 next morning	100		1.024

TABLE 4.—*Data on Water Excretion of S. J.*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
9/27/24	49	7- 8	200		1.024
		8- 9	36		1.024
		9-10	55	Sum	1.022
		10-11	23	154	1.011
		11-12	40		1.017
		12- 6	45		1.018
		6- 7	0		
		7- 6	0		
		6- 7 next morning	32		1.023
10/30/24	81	7- 8	104		1.018
		8- 9	78		1.014
		9-10	470	Sum	1.004
		10-11	265	885	1.006
		11-12	72		1.016
		12- 6	0		
		6- 7	83		1.021
		7- 6	0		
		6- 7 next morning	24		1.021

shows a normal or almost normal result, and also the reverse. An example of the first case will be seen in table 6; in the patient concerning whom data are given, there was a slightly noticeable edema with a positive compression reaction on the arms and legs.

An example of a different course is shown in table 7 in a case in which the excretion of water was greatly reduced in spite of the lack of evidence of manifest or occult edema.

TABLE 5.—*Data on Water Excretion of L. M.*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
6/ 4/24	76	7- 8	104		1.019
		8- 9	212		1.007
		9-10	450	Sum	1.005
		10-11	180	900	1.007
		11-12	58		1.015
		12- 6	290		1.014
		6- 7	49		1.023
		7-6	310		1.024
		6- 7 next morning	46		1.022
3/ 5/25	40	7- 8	41		1.020
		8- 9	25		1.020
		9-10	44	Sum	1.020
		10-11	52	171	1.018
		11-12	50		1.012
		12- 6	370		1.013
		6- 7	80		1.016
		7- 6	470		1.018
		6- 7 next morning	32		1.020

TABLE 6.—*Data on Water Excretion of J. C.*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
3/10/25	32	7- 8	86		1.013
		8- 9	315		1.004
		9-10	365	Sum	1.004
		10-11	57	774	1.013
		11-12	37		1.015
		12- 6			
		6- 7	26		1.016
		7- 6			
		6- 7 next morning	25		1.017

It seems that the excretion of water can give a more definite indication of the actual condition than the edema, which is either in a stage of development or in a stage of resorption.

CAUSES OF EDEMA AND REDUCTION IN THE EXCRETION OF WATER

Cardiac Insufficiency.—In an article published in 1905, Kraus[8] says that he tried to determine, by means of clinical and experimental

8. Kraus: Berl. klin. Wchnschr., vol. 4, 1905.

data, the influence of fatty degeneration on the functional power of the heart. His attempt, however, was without much result. He concludes that: "alles in allem müssen wir uns am Krankenbett doch wohl eher auf den Standpunkt derjenigen stellen, welche die degeneratio adiposa cordis, zumal bei gleichzeitig dauernd erhöhter Arbeit des Herzens, auch in den mittleren Graden mit Bezug auf die Leistungsfähigkeit keineswegs für völlig bedeutungslos halten." (Doubtless we must take the clinical attitude of those who consider degeneratio adiposa cordis [even though only a moderate degree], especially if associated with increased work of the heart, as exerting considerable influence on its performance.)

However, the question appears doubtful. Clinically, these patients do not have any positive indication of cardiac insufficiency; the dyspnea and tachycardia observed when the patient walks about are well accounted for by the lowered amount of hemoglobin with its accompany-

TABLE 7.—*Data on Water Excretion of P. N.*

Date	Hemoglobin Percentage	Time	Diuresis		Specific Gravity
1/19/25	42	7– 8	55		1.017
		8– 9	43		1.017
		9–10	50	Sum	1.019
		10–11	40	169	1.019
		11–12	36		1.019
		12– 6	290		1.017
		6– 7	36		1.019
		7– 6	530		1.019
		6– 7 next morning	78		1.016

ing lack of oxygen, and need not indicate a definite weakening of the heart muscle. When a patient is at rest and in bed, these symptoms are not evident in spite of definite edema. More important, however, is the fact that other stasis phenomena are lacking: hypostasis pulmonum, stasis hepatis and stasis renum. Furthermore, in its localization the edema does not resemble cardiac edema. It is more diffuse and often appears with edema of the face. We are prone to be reserved in placing too great stress on the influence of a weakened functional power of the heart in the pathogenesis of edema or the reduction of the excretion of water.

Nephropathy.—That edema or the reduction in the excretion of water may be caused by a renal disturbance is a possibility that has received much more attention; recently, the majority of those who have studied this question have come to the conclusion that the symptoms are renal. The fact is that the kidneys often are actually the site of slight pathologic anatomic changes sometimes accompanied by a slight change in the function of the kidney. Anatomically, the kidneys (Makarow,[1] Saltzman[2]) are seldom normal, and they are often the site of mild

parenchymatous as well as interstitial changes. As a rule, the changes are not definite, and they are comparatively seldom seen macroscopically. When seen, they consist of a slight shrinkage of the kidney, a slight roughness and granulation of its surface, a small adherent capsule and a rather small cortex. Microscopically a more or less extensive fatty infiltration of the epithelia, other degenerative processes in the epithelia and slight changes in the glomeruli with an increase in the interstitial tissue are found. In some cases, these changes are evident and pronounced, doubtlessly the reason for the former number of publications on the simultaneity of pernicious anemia and chronic nephritis. Saltzman [2] concluded that "The histological data indicates that in pernicious anemia nephrosis goes hand in hand with interstitial and glomeruli changes."

There are manifold data concerning the function of the kidneys. In the first place it is a long established fact that albuminuria, although mild and, as a rule, transitory, is often a symptom of the disease. There is, however, a difference of opinion concerning the frequency of albuminuria. It is most frequently reported by Cabot,[6] who found albuminuria in 236 of 506 cases (40 per cent) and cylindruria in 119 cases (24 per cent). Saltzman [2] reported albuminuria in seven of eleven cases. He stated that it was not decidedly marked and was usually transitory, the greatest quantity observed being one per thousand.

Retention of nitrogen has been the subject of much research. Kahn and Barsky [9] found a normal amount of nonprotein nitrogen and blood urea in three cases and a normal function of the kidneys as determined by the phenolsulphonphthalein test. Gettler and Lindeman [10] examined thirty-two patients with pernicious anemia and found that in 12 per cent the amount of nonprotein nitrogen was over 60 mg. per hundred cubic centimeters and that in 18 per cent, the blood urea was over 40 mg. per hundred cubic centimeters. This high percentage was obtained from comparatively few cases. Essen and Porges [5] examined ten patients with pernicious anemia and found that the amount of nonprotein nitrogen was normal or nearly normal.

We examined the function of the kidneys in our patients partly by examining the urine for albumin and cylindroids, partly by the thiosulphate test and partly by van Slyke's blood urea test. We also took the systolic blood pressure (Riva-Rocci).

Our examinations of the urine showed a slight trace of albumin, as a transitory phenomena, in eleven of thirty-seven patients; in the

9. Kahn and Barsky: Chemistry of Pernicious Anemia, Arch. Int. Med. **23:** 334 (March) 1919.

10. Gettler and Lindeman: Blood Chemistry of Pernicious Anemia, Arch. Int. Med. **26:**453 (Oct.) 1920.

urine of four there were a few cylindroids. In addition, six patients who had degeneration of the spinal cord with cystitis or cystopyelitis, had pyuria and gave a positive reaction to the test for albumin. The urine of each patient was examined a number of times, but it is possible that had we examined it more often, the number of cases in which albumin and cylindroids were present would have been greater. The main point, however, is that albuminuria was always a transitory phenomena, and that there was only a slight trace of albumin.

As a rule, the thiosulphate test was made with the water test. The results are summed up in table 8.

If the normal limit excretion of thiosulphate is placed at 20 per cent, it will be seen that the excretion usually is normal. Seventeen determinations were slightly under this limit. In four of these, either a little of the thiosulphate was not injected into the vein, or the urine was voided three hours instead of four hours after the injection, making it impossible to complete the titering. It is possible that these four cases

TABLE 8.—*Results of Thiosulphate Test with Water Test*

Thiosulphate excretion percentage.....	>25	25-20	20-15	15-10	<10
Number of patients.....	34	32	17	3	2

TABLE 9.—*Blood Urea Determinations*

Blood urea in mg., percentage.....	<30	30-40	40-50	50-60	>60
Number of patients.....	34	25	21	1	5

would be above the 20 per cent limit. The remainder, as a rule between 18 and 19 per cent, are divided among normal determinations made on the same patient. There were five determinations under 15 per cent. Four of these were made in two cases. Both of the patients had degeneration of the spinal cord with sphincteric disorder and pyuria. Judged by the thiosulphate test, we concluded that in uncomplicated cases of pernicious anemia there is only a doubtful or insignificant decrease in the function of the kidneys.

Next, the blood urea must be considered. The eighty-six determinations are summed up in table 9. Twenty-one of the determinations were at the maximum of the normal limit. It is doubtful, however, whether this is an indication of a pathologic condition. Six of the determinations were beyond the maximum of the normal limit. The tests were made on the same patient, a man with hydrops. Macroscopic and microscopic examination of sections showed fibrous changes in the kidneys. It is worthy of note that in this case there was either no decrease in the thiosulphate excretion or a doubtful decrease, a circumstance that we cannot explain. We also determined the blood urea

in four cases in which the water test or thiosulphate test had not been performed. The first patient had abnormally high determinations, 83 and 73 mg. per hundred cubic centimeters, incontinence of urine and pyuria. Macroscopic and microscopic examination of sections of the kidneys showed moderately pronounced fibrous changes. The last patient also had an abnormal determination, 66 mg. per hundred cubic centimeters the day before death.

Finally, the blood pressure must be considered. As a rule, the determinations were low. In two instances, there was hypertension. Consequently, it can be considered that the blood pressure is usually low.

In summary: The tests show that generally there is not a noticeable kidney insufficiency, but that, as a rule, the function of the kidneys is good. It would seem unusual if nephropathy could be a determining factor in the origin of edema or the reduced excretion of water. Furthermore, Krogh,[11] Hagedorn and Rasmussen and Rehberg [12] have pointed out that typical nephrotic edema accompanies albuminuria, as the blood's colloid osmotic pressure is lowered by the protein loss because the small and more osmotic active protein molecules preferably are eliminated through the kidneys. A large protein loss of this kind is never observed in pernicious anemia.

Hemoglobin Content.—The next question is, how great is the significance of the anemia itself, i.e., the low hemoglobin content in the production of symptoms? Essen and Porges [5] expressed the opinion that the kidneys, as far as the excretion of water is concerned, adapt themselves to the hemoglobin insufficiency by excreting an isotonic urine.

Our data show that edema and reduced excretion of water do not always occur when the hemoglobin content is low. Of course, both the phenomena are present during relapses and disappear during the remissions, but in many instances, there is a noteworthy incongruity. We often found a satisfactory four hour excretion of water when the amount of hemoglobin was less than 50 per cent; on the other hand, we never found a reduced excretion, when the hemoglobin content was more than 50 per cent.

To be able to determine whether the low hemoglobin content causes these symptoms, we used the water test in cases of posthemorrhagic anemia. We chose this type because in other types of anemia (leukemia, cancer, etc.) a toxic factor may be present which could complicate the experiment. Unfortunately, we had only twelve cases of posthemorrhagic anemia at our disposal for the experiment. None of the patients had edema and eleven (table 10) had a normal excretion of

11. Krogh: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922.

12. Hagedorn, Rasmussen and Rehberg, cited in Krogh (footnote 11).

water in four hours with a pronounced change between the greatest dilution and the greatest concentration. These observations do not indicate that the low hemoglobin content is of great significance as a cause of edema and reduction in the excretion of water.

Osmotic Pressure in the Plasma.—Finally, we turned our attention to the plasma colloids and the colloid osmotic pressure in the plasma to determine whether a lowered amount of total protein and a lowered colloid osmotic pressure in the plasma could cause the edema and reduction in the excretion of water. Jaksch [13] and Grawitz [14] reported the occurrence of a small amount of total protein in the plasma. Erben [15] reported one case in which there was 5.2 per cent total protein in the plasma, 4.2 per cent albumin and 1 per cent globulin with 15 per cent hemoglobin. Kahn and Barsky [9] found a small amount of total protein in the plasma in three cases of pernicious anemia. Gettler and Linde-

TABLE 10.—*Data on Water Excretion in Twelve Cases of Posthemorrhagic Anemia*

Diagnosis	Hemoglobin Percentage	Four Hour Excretion	Lowest Specific Gravity	Highest Specific Gravity
Melena	34	885	1.005	1.019
Anemia following abortion	57	994	1.004	1.026
Melena	44	1,070	1.003	1.027
Anemia following abortion	54	1,296	1.003	1.024
Hematemesis	34	715	1.008	1.025
Anemia following abortion	40	1,143	1.007	1.025
Melena	40	537	1.007	1.029
Melena	45	1,085	1.008	1.029
Anemia following abortion	55	710	1.004	1.022
Anemia following extraction of teeth	50	1,315	1.001	1.029
Melena	35	760	1.005	1.025

man [10] reported the cases of thirty-two patients who had pernicious anemia and found that the refraction determinations in three fourths of them showed that the serum was below normal, and in some they found that the amount of total protein was smaller than in cases of severe nephrosis with edema. This decrease at times was from 40 to 50 per cent below the normal determinations. The specific gravity was proportionately lowered, so that 80 per cent of the determinations were below normal. Essen and Porges [5] also found low refraction. Naegeli,[16] however, reported the opposite. In his textbook, he said: "Das Serumeiweiss ist meist in ungefähr normaler Menge (7-8% Eiwess) vorhanden, wie ich durch hunderte von refraktometrischen Untersuchungen ersehen habe. Eine Hydramie besteht also im allgemeinen nicht. Erst bei

13. Von Jaksch: Ztschr. f. klin. Med. **23**:186, 1892.

14. Grawitz: Berl. klin. Wchnschr. **35**:704, 1898; Klinische Pathologie des Blutes, Leipzig, 1911, p. 435.

15. Erben: Ztschr. f. klin. Med. **40**:266, 1900.

16. Naegeli: Blutkrankheiten und Blutdiagnostik, Berlin, 1923, p. 312.

akuter Verschlechterung sinkt der Eiweissgehalt. Bleibt jedoch der Patient längere Zeit auf dem niedrigen Hb-wert, so stellt sich auch der Eiweissgehalt wieder auf die Norm ein. Die Globuline stehen in der Mehrzahl der Fälle an der oberen Grenze der Norm (um 40%), zeigen in einzelnen Beobachtungen aber auffällig niedrige Werte." (The protein value of the serum is generally about normal [from 7 to 8 per cent albumin], as I have seen in hundreds of refraction tests. Hence hydremia is not usually present. Only in association with an acute exacerbation does the protein content become lower. If, however, the hemoglobin value is low for some time, the protein content again becomes normal. The globulin content in the majority of cases is at the highest normal limit [about 40 per cent], but in rare cases unusually low values are seen).

The fibrinogen has been given much study by Drinker and Hurwitz.[17] They found a few patients with a normal amount in the plasma. Rusznyak, Barat and Kurthy[18] found a high fibrinogen content with normal albumin and globulin determinations in some cases, and H. C. Gram,[19] who made an exhaustive study of the subject, found a pronounced tendency toward low determinations.

Of the foregoing research work, Gettler's and Lindeman's[10] is the most comprehensive. According to their data, a lower amount of total protein is to be expected in severe cases.

In determining the pathogenesis of edema, however, it is of the greatest importance and interest to know whether there is lowered colloid osmotic pressure in the blood. Positive proof of this was obtained in only one case, reported by Mayrs,[20] who found a colloid osmotic pressure of 264 mm. of water in the serum, a total protein amount of 6.0375 per cent and a colloid osmotic pressure of 43.7 per gram of albumin. There was no edema, and there is no mention of the percentage of hemoglobin. His normal determinations for the foregoing factors were 402, 7.875 and 51, respectively.

We determined the amount of total protein and the colloid osmotic pressure in the serum of eleven patients with pernicious anemia, and in one patient with anemia caused by pregnancy and resembling pernicious anemia (table 11).

We used Pulfrich's refractometer for the refraction in determining the total protein in the serum. The normal determinations as given by Reiss[21] vary from 7 to 9 per cent, those of Naegeli[16] from 7 to 9.1 per

17. Drinker and Hurwitz: The Factors of Coagulation in Primary Pernicious Anemia, Arch. Int. Med. **15**:733 (May) 1915.
18. Rusznyak, Barat and Kurthy: Ztschr. f. klin. Med. **98**:337, 1924.
19. Gram, H. C.: Disputats, Copenhagen, 1921, p. 89.
20. Mayrs: Quart. J. Med. **19**:273, 1926.
21. Reiss: Verhandl. d. Versamml. deutsch. Naturr. u. Aerzte., 1904, p. 36.

TABLE 11.—*Eleven Patients with Pernicious Anemia and One with Anemia of Pregnancy*

No.	Date	Name	Age	Hemoglobin %	Edema	Water Excretion: Four Hours' Excretion	Water Excretion: Highest Specific Gravity	Water Excretion: Lowest Specific Gravity	Serum Protein Percentage	Colloid Osmotic Pressure in Mm. of Water	Colloid Osmotic Pressure per Gm. Protein in Mm. of Water	Remarks
1	10/23/26	Mr. N. Son.	58	23	Slight edema of the face, moderate edema of the lumbar region, slight edema of hands and legs	...	.....	.....	5.94	324.0	54.4	
2	11/18/26	Mr. J. M. Mak.	55	51	÷	...	.....	.....	5.90	285.0	48.3	Blood transfusion 3 weeks previous
	12/13/26		..	50	÷	...	.....	.....	6.77	306.0	45.2	
3	11/18/26	Mrs. R. Ko.	71	86	Edema of the lumbar region . occult edema	360	1.016	1.012	7.31	289.0	39.2	
	3/15/27		..	40	Slight edema of the lumbar region...	181	1.017	1.006	6.98	285.0	40.8	
4	11/18/26	Mrs. N. Gar.	72	57	÷	...	.....	.....	6.98	280.0	40.1	
	4/28/27		..	42	Slight edema of the lumbar region, minimal occult edema	205	1.019	1.015	6.51	263.5	40.5	
5	3/15/27	Mrs. B. Geh.	59	59	Trace of edema of the legs, occult edema	820	1.024	1.006	6.98	310.0	44.4	
	4/28/27		..	67	Slight edema of the lumbar region, slight edema of the legs, occult edema	505	1.020	1.006	6.91	321.5	46.5	Spinal degeneration
6	3/30/27	Mrs. L. A. Jen.	72	50	Slight edema of the lumbar region, trace of occult edema	660	1.020	1.007	7.20	299.0	41.6	
	4/28/27		..	43	Edema of the lumbar region, slight edema of the legs, occult edema	310	1.015	1.010	5.90	247.0	42.0	
7	4/28/27	Mrs. E. A. Pet.	44	15	Edema of the lumbar region, marked edema of the legs	...	.....	.....	5.70	248.0	43.5	
8	4/28/27	Miss E. Hill.	48	50	Trace of edema of the lumbar region, trace of edema of the legs, occult edema	530	1.021	1.007	7.12	284.0	39.9	
9	4/28/27	Mrs. K. E. Tho.	35	32	Edema of the face, edema of the lumbar region, edema of the legs	175	1.017	1.012	5.90	279.0	47.2	Blood transfusion 1 week previous
10	5/ 4/27	Mr. O. Pet.	50	35	Trace of occult edema	...	.....	.....	5.90	296.0	50.5	Blood transfusion 1 week previous
11	5/ 4/27	Mr. J. P. Ro.	59	55	÷	615	1.028	1.010	6.91	338.5	49.0	
12	3/ 8/27	Mrs. M. Pet.	40	11	Visible edema of the face, marked edema of the lumbar region, moderate edema of the legs	...	.....	.....	5.90	253.0	42.9	Anemia of pregnancy

cent, while in a small number we found that it varied from 6.98 to 8.28 per cent. We determined the serum's colloid osmotic pressure with Krogh's osmometer. The determinations were made under Professor Krogh's direction at the Animal Physiological Laboratory. None of the patients had any indication of heart disease; there was no albuminuria nor increased blood pressure.

In looking first at the total protein in the serum, conformity with the foregoing results will be seen, as there is a lowered amount of total protein. A proportionately lower amount of protein was found in other patients with pernicious anemia. The decrease was pronounced, but not as extreme as in some nephrotic patients.

The colloid osmotic pressure of the serum is also lower. Our normal determinations varied from 401 to 325 mm. of water with an average of 362, and in patients with pernicious anemia, from 324 to 248. This decrease is moderate, as we did not find the determinations as low as in patients with nephrosis, who in severe cases have a colloid osmotic pressure as low as 80 (Iversen and Nakazawa [22]).

Finally, in the last column is the colloid osmotic pressure per cent total protein. Here our normal determinations varied from 54 to 44, with 47.4 as an average, not differing from the pressure found in cases of pernicious anemia; this makes it evident that the lowering of the colloid osmotic pressure is proportional to the lowering of the amount of protein, or that this decrease is dependent on the quantitative and not on the qualitative changes in the plasma colloids. In other words, the reduction in protein affects the larger molecular and the smaller molecular plasma colloids to the same extent.

There is a decided difference in this respect in nephrotic patients, whose colloid osmotic pressure according to the percentage of albumin is lowered because the smaller molecular plasma colloids lost in the kidneys cause a relative increase of the larger molecular plasma colloids in the blood.

The question now is whether this lowered amount of total protein and the moderate decrease in the colloid osmotic pressure can be the source of the edema and the reduction in the excretion of water in pernicious anemia.

In nephrotic patients, we found that the critical zone was between 270 and 240 mm. of water. In this zone, the colloid osmotic pressure has a tendency to be the same or lower than the hydrostatic pressure in the capillaries. Some of our determinations in pernicious anemia are in this critical zone. This justifies us in believing that the low amount of protein and the low colloid osmotic pressure in the blood may be a contributing factor in the cause of edema in pernicious anemia,

22. Iversen and Nakazawa: Biochem. Ztschr. **191**:307, 1927.

and that in some cases it possibly is the dominating influence. Unfortunately, we have not had occasion to examine patients with the greatly pronounced edema occasionally found in extreme cases of pernicious anemia, but it is probable that in such cases a great reduction in the amount of protein and in the colloid osmotic pressure would be found.

There is reason to believe, however, that there is still one factor, maybe more, which is instrumental in the pathogenesis of edema and the reduction in the excretion of water. This seems to be true because there is no consistent parallelism between the amount of edema and the reduction in the excretion of water on the one hand, and the lowering of the colloid osmotic pressure on the other; one may find pronounced edema with a colloid osmotic pressure well above the critical zone. It seems to be true also because there is one fact not yet explained, namely, in posthemorrhagic anemia there is no edema or reduction in

TABLE 12.—*Data on Colloid Osmotic Pressure in Three Patients with Posthemorrhagic Anemia*

No.	Date	Name	Age	Hemoglobin Percentage	Edema	Serum Protein Percentage	Colloid Osmotic Pressure in Mm. Water	Colloid Osmotic Pressure per Gm. Protein in Mm. Water	Remarks
1	10/28/16	Mr. T. G.	34	50	+	6.46	272	42.2	Melena
2	11/15/26	Mr. H. P. P.	55	45	+	5.90	250	42.4	Melena
	12/ 6/26			40	+	5.68	264	46.5	Melena
	12/18/26			40	+	6.12	277	45.2	Melena
3	12/ 1/26	Mr. C. A.	27	35	+	6.34	277	43.6	Melena
	12/ 8/26			46	+	6.55	318	48.6	Melena

the excretion of water in most instances. Table 10 shows that there was no indication of edema or a reduction in the excretion of water among the patients with posthemorrhagic anemia. In some cases of the same type and intensity examined (table 12), it was observed that the colloid osmotic pressure was lowered and remained at the same level as in pernicious anemia. This point requires more study, but our research indicates that there may be some other factor.

This factor may possibly be weakness of the heart with the consequent increase of hydrostatic pressure in the capillaries. Or there is a possibility that in pernicious anemia, during the severe periods, there may be a metamorphosis in the capillary walls and an increased permeability for the plasma colloids.

From one patient we were fortunate enough to obtain about 2 cc. of edematous fluid, which, on examination, was found to contain 1.1 per cent of total protein; the colloid osmotic activity, however, was not determined. This is rather a large protein content, but in using such small amounts of edematous fluid, mistakes undoubtedly may occur

through mechanical injury to the capillaries. It is perhaps worthy of mention that Hess and Müller,[23] in experiments with anemia caused by blood poisons, pyrodine and toluylendiamine, found edema in the experimental animals, and that the edematous fluid from the pleurae of these animals showed a high protein content (up to 6 per cent) which the authors think was due to a toxic injury and increased permeability of the endotheliums.

SUMMARY

1. In pernicious anemia, edema frequently occurs, and the water test often shows a reduction in the excretion of water.

2. These symptoms are present during a relapse and disappear during a remission.

3. It does not seem probable that the symptoms are caused by impairment of the function of the kidneys or by the anemic condition, the low amount of hemoglobin.

4. In many instances a decrease in the total protein with a lowering of the colloid osmotic pressure in the plasma was found.

5. The lowered colloid osmotic pressure often occurs in the critical zone of the origin of the edema, and may therefore be a contributing cause in the production of edema and probably as well of the reduction in the excretion of water in pernicious anemia. One or more additional factors must also be present, however, possibly dilatation of the heart or an increased permeability of the capillary walls.

23. Hess and Müller: Wien. klin. Wchnschr. **27**:121, 1914.

LORDOSIS AS A CAUSE OF POSTURAL ALBUMINURIA *

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In the course of a study of various types of benign albuminuria, we have had an opportunity to study thoroughly the so-called postural albuminuria, in which albuminuria becomes manifest in certain persons if they assume the upright position and disappears if they assume the recumbent position. This type of benign albuminuria is also spoken of as orthostatic or orthotic albuminuria.

Concerning this condition, there is still much controversy regarding the factors of its production and causation. Maxon,[1] who gave the earliest description of the condition, called attention to the fact that the albuminuria was apparently not associated with evidence of renal disease. He distinguished an albuminuria of adolescence with a fairly permanent showing of albumin in the urine and a remittent type in which the albumin completely disappeared from the urine when the subject was recumbent and reappeared after assumption of the erect posture. Pavy [2] reported a similar group of cases. Stirling [3] first emphasized the importance of posture and its definite connection with the appearance and disappearance of the albumin in the urine. Heubner [4] suggested the term "orthotic" and Tissier [5] the term "orthostatic."

The effect of exaggerated lordosis as a factor in the development of postural albuminuria was not stressed until Jehle [6] published his exhaustive study on this condition. He was so impressed with the connection between the two that he suggested the term "lordotic albuminuria." Nassau,[7] however, pointed out that there were two distinct types of postural albuminuria, a type occurring without any lordosis and a type occurring in connection with exaggerated lordosis.

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1. Maxon, W.: Guy's Hosp. Rep. **23**:233, 1878.
2. Pavy, F. W.: Brit. M. J. **2**:789, 1885.
3. Stirling, A. W.: Lancet **2**:1157, 1887.
4. Heubner, O.: Ueber chronische Nephritis und Albuminuria im Kindersalter, Berlin, A. Hirschwald, 1897.
5. Tissier, H.: Semaine méd. **19**:245, 1899.
6. Jehle, B.: Die lordatishe Albuminuria, Berlin, Julius Springer, 1914
7. Nassau, E.: Ztschr. f. Kinderh. **33**:158 (Aug.) 1922.

Various theories have been advanced as to the cause of postural albuminuria. Erlanger and Hooker [8] believed that diminished pulse pressure was the cause and that the amount of albumin excreted varied inversely to the magnitude of pulse pressure. Mason and Erickson,[9] Bass and Wessler [10] came to similar conclusions. Tissier [5] advanced the theory that the developmental defects of the glomeruli, with consequent increased permeability of the kidney, were the responsible factor. Jehle [6] believed that mechanical interference with the renal circulation, such as is possible through the effect of marked lordosis, was the sole

Result of Daily Urinalyses in Twenty-Five Cases of Lordosis Over a Period of Six Months

Case	Age	Sex	Type of Deformity	Deformity Due to	Urinalysis: Albumin A. M.	Urinalysis: Albumin P. M.	Urinalysis: Microscopic
1	14	M	Lordosis, scoliosis	Poliomyelitis	0	0	All negative
2	6	F	Lordosis, scoliosis	Poliomyelitis	0	0	All negative
3	6	F	Lordosis	Congential spastic deformity	0	0	All negative
4	7	F	Lordosis	Poliomyelitis	0	0	All negative
5	7	M	Lordosis, tilting of pelvis	Rickets	0	++	All negative
6	14	F	Lordosis	Poliomyelitis	0	0	All negative
7	8	M	Lordosis, pelvic deformity	Poliomyelitis	0	0	All negative
8	9	M	Lordosis	Poliomyelitis	0	0	All negative
9	11	F	Lordosis	Poliomyelitis	0	0	All negative
10	12	F	Lordosis	Poliomyelitis	0	+	All negative
11	12	F	Lordosis, scoliosis	Poliomyelitis	0	0	All negative
12	11	M	Lordosis	Poliomyelitis	Trace	++	All negative
13	16	F	Kyphoscoliosis, lordosis	Rickets; muscu-latrophy	Inconstant orthostatic albuminuria		
14	11	F	Lordosis	Spastic paralysis	0	0	All negative
15	8	M	Scoliosis, lordosis	Poliomyelitis	0	0	All negative
16	19	F	Lordosis, pelvic deformity	Poliomyelitis	0	0	All negative
17	18	F	Lordosis	Poliomyelitis	0	0	All negative
18	15	F	Lordosis	Poliomyelitis	0	+	All negative
19	9	M	Scoliosis, lordosis	Rickets	0	0	All negative
20	8	F	Scoliosis, lordosis	Poliomyelitis	0	0	All negative
21	6	F	Lordosis	Poliomyelitis	Inconstant albuminuria		
22	11	M	Lordosis	Spastic paralysis	0	0	All negative
23	7	F	Lordosis	Poliomyelitis	0	0	All negative
24	14	M	Lordosis	Poliomyelitis	0	0	All negative
25	12	M	Lordosis, scoliosis	Poliomyelitis	0	0	All negative

cause: Acute renal venous stasis ensues with retardation of venous circulation. Owing to anatomic peculiarities, this stasis is more pronounced on the left side than on the right side.

However, Goetsky's [11] careful observations, confirmed since by many observers, indicated that as a cause, exaggerated lordosis is probably

8. Erlanger, J., and Hooker, D. R.: Johns Hopkins Hosp. Rep. **12**:145, 1904.

9. Mason, E. H., and Erickson, R. J.: Am. J. M. Sc. **156**:64, 1918.

10. Bass, M. H., and Wessler, Harry: A Study of the Blood Pressure in Children Showing Orthostatic Albuminuria, Arch. Int. Med. **13**:39 (Jan.) 1914

11. Goetsky, F. K. H.: Zur Kenntnis der orthotischen Albuminuria, Diss. Berlin, August, 1910.

unimportant. Extended series of cases in which lordosis was pronounced, did not show albuminuria and, again, cases in which lordosis was not present, showed a large amount of albumin on change of posture.

In our study of postural albuminuria, we had frequently found it difficult to determine, to our satisfaction, whether the orthostatic albuminuria was due definitely to a lordotic condition or to some other factors. Since there is no way of determining with certainty what degree of malposture constitutes a deviation from the normal, we decided to select for our study, cases of unusually pronounced lordotic deformity.

We therefore selected a group of twenty-five crippled children and young adults. In nineteen of this group, the deformity was due to a residual paralysis of poliomyelitis; three children had had severe rickets in infancy; in three others, the deformity was the result of a congenital, spastic paralysis. The types of deformities were those of simple lordosis and of lordosis associated with various degrees of scoliosis of the dorsal and lumbar spine.

The patients were observed for six months. All urinalyses were made on morning and afternoon specimens. The mothers were instructed to collect the specimens of urine before the children got out of their beds. Only those cases in which microscopic observations in the routine urinalyses were persistently negative were included in this group. The urine was alkalinized in the cases of positive albuminuria and the effect on the excretion of albumin studied. In two cases of persistent orthostatic albuminuria, the plasma proteins (fibrin, globulin, albumin), amino-acids and urea nitrogen were determined.

COMMENT AND CONCLUSION

Contrary to our expectation, out of this group of twenty-five definitely lordotic children only three showed a persistent tendency to the orthostatic type of albuminuria. This, we find, is not higher, proportionally, than in other groups of postural albuminuria without definite lordosis. Three others showed the tendency inconstantly. Removal of orthopedic appliances was followed by no observable change in the excretion of albumin. Alkalinization of urine did not have any particular effect on the excretion of albumin. The blood chemistry did not show any essential deviation from the normal, which agrees with the observations of Schlutz and Swanson.[12]

As a result of our observations, we believe that exaggerated lordosis is an unimportant factor in the production of orthostatic albuminuria.

12. Schlutz, M. F., and Swanson, W. W.: The Plasma Protein in Postural Albuminuria, J. A. M. A. **87**:1193 (Oct. 9) 1926.

THE DEXTROSE-TOLERANCE TEST

ITS USE IN THE DETERMINATION OF THE SEVERITY OF DIABETES MELLITUS *

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When there is a disturbance in the functioning of an organ, appearing either as hyperfunction or hypofunction, it is desirable in most instances to be able to determine the degree of derangement. In diseases of the thyroid, for instance, the basal metabolism can be calculated with mathematical exactness; the state of functional activity of that organ can be determined. In heart disease, however, one must be content with a classification such as that proposed by the New York Society for the Study of Cardiac Diseases. For other organs, tests have been devised, some of which accurately and some inaccurately portray the functional activity of the organ. This paper is devoted to a study of some of the methods used to determine the severity of diabetes mellitus.

Joslin,[1] in his textbook on "Treatment of Diabetes Mellitus," suggests the following classification: (*a*) severe cases—those in which the patients are able to metabolize from 0 to 10 Gm. of dextrose daily, (*b*) moderate cases—those in which they are able to metabolize from 11 to 50 Gm. and (*c*) mild cases—those in which they are able to metabolize more than 50 Gm. By dextrose is probably meant the dextrose value of all foods metabolized. All of the carbohydrates may be estimated as convertible wholly into dextrose. Fifty-eight per cent by weight of protein is converted into sugar, as has been determined by Lusk from studies on phlorizinized dogs. According to Woodyatt,[2] the glycerin fraction of fat may be considered as dextrose and is equal to one-tenth by weight of the fat. Macleod [3] considers the question of dextrogenesis from fat as not settled. The dextrose value of foods may be tersely expressed in the following formula:

$$D = 1C + .58P + .1F$$

Another term which should be defined at this point is "dextrose balance."

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1. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, 1923, p. 483.

2. Woodyatt, R. T.: Objects and Methods of Diet Adjustment in Diabetes Mellitus, Arch. Int. Med. **28**:125 (Aug.) 1921.

3. Macleod, J. J. R.: Carbohydrate Metabolism and Insulin, New York, Longmans, Green & Company, 1926, p. 123.

By this is meant the difference between the amount of carbohydrate ingested and the amount of dextrose excreted in the urine. It is evident that if the "dextrose balance" is to have any significance, the patient must be in nitrogenous and caloric equilibrium. Even then one is uncertain as to whether only the food ingested was metabolized.

To Woodyatt [2] foods are of significance in diabetes mellitus only so far as they give rise to dextrose or fatty acids. He attributes to the internal secretion of the pancreas, so far as metabolism is concerned, but one function: the control of the metabolism of carbohydrates.

He illustrates his conception by a study of one case (table 1). The patient was put successively on diets 1, 2 and 3. On diet 1, which had a dextrose value of 159, he excreted 50 Gm. of dextrose. This gave a dextrose balance of 109 Gm. Diets 2 and 3 were entirely

TABLE 1.—*The Dextrose Balance Produced with Different Test Diets in a Case of Diabetes Mellitus, Observed by Woodyatt*

Diet	Carbohydrate	Protein	Fat	Total Calories	Dextrose Value	Dextrose Excreted	Dextrose Balance
1	92	103	70	1,436	159	50	109
2	84	11	162	1,836	116	0	116
3	28	118	130	2,054	112	0	112

TABLE 2.—*Wilder's Observations of the Dextrose Balances in a Case of Diabetes Mellitus Under Influence of Test Diets*

Diet	Carbohydrate	Protein	Fat	Units of Insulin	Dextrose Value	Calories	Dextrose Excreted	Dextrose Balance	Blood Sugar
1	112	45	142	15	152	1,956	9.5	142.5	0.22
2	41	150	118	15	145	1,907	47	98	0.28

different from diet 1, in respect to both total number of calories and the proportions of the various foods. Diets 2 and 3 did not cause glycosuria. This gave dextrose balances of 116 and 112, respectively, which were almost equal to the dextrose balance produced with diet 1. Woodyatt concludes that dextrose is the sole food of importance in diabetes mellitus, and that it matters little whether the dextrose is derived from proteins, carbohydrates or fats. If we are to accept his conception, then the classification of Joslin, mentioned previously, is sound. One strong criticism may be offered: the patient was not in either caloric or nitrogenous equilibrium. Under these circumstances, little significance could be attached to the dextrose balances.

Wilder and his collaborators,[4] from the study of a case (table 2), reach conclusions that are completely at variance with those of Woodyatt.

4. Wilder, R. M.; Boothby, W. M.; Baborka, C. J.; Kitchen, H. D., and Adams, S. F.: Clinical Observations on Insulin, J. Metab. Research **2**:701, 1922.

Diets 1 and 2 were isocaloric and isosaccharin; in diet 1, most of the dextrose was derived from carbohydrates, and in diet 2 from proteins. With each diet the patient received 15 units of insulin. On diet 1, he excreted 9.5 Gm. of dextrose, giving a dextrose balance of 142.5 Gm. On diet 2, he excreted 47 Gm., giving a dextrose balance of 98 Gm. It is not within the scope of this paper to discuss the reasons for these results. They definitely contradict the conclusions of Woodyatt.

Of great importance is the work of Allen [5] on the influence of fat and total number of calories on diabetes and on the requirement of insulin. He has shown that an increase in the amount of fat in the diet raises the insulin requirement out of all proportion to the amount of sugar derived from the fat. An increase in the total number of calories has a similar effect. He concludes that insulin is concerned with the metabolism of all foods—carbohydrate, protein and fat—

TABLE 3.—*Comparison of Diets Used by Joslin with Those Used by Newburgh and Marsh*

(a) Joslin's Diets	Carbohydrate	Protein	Fat	Calories
Test diet 1	181	46	44	1,304
2	101	35	43	931
3	66	24	37	693
4	34	15	30	466
Maintenance diet no. 12	159	84	135	2,187
(b) Newburgh and Marsh Diets				
	14	10	90	900
	15-20	28	140	1,400
	25-30	30-40	170	1,800

and with anabolic as well as catabolic processes. He stresses also the paradoxic so-called "law of dextrose," namely, that the increment in the dosage of dextrose is always greater than the increment of excretion. The test and maintenance diets employed by Joslin [6] are utterly different in the proportion of the various foods from those utilized by Newburgh and Marsh [7] (table 3).

It is evident that a classification of diabetes which takes into account only the dextrose of the diet of a patient who is on a mixed diet is fallacious.

Joslin [1] proposes another classification, which is more in conformity with the work of Wilder [4] and Allen.[5] It is based on the requirement of insulin when the patient is ingesting 1 Gm. of carbohydrate, 1 Gm. of protein and 2 Gm. of fat per kilogram of body weight. If insulin

5. Allen, F. M.: Influence of Fat and Total Calories on Diabetes and the Insulin Requirement, J. Metab. Research **3**:61, 1923.

6. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, 1923, p. 493.

7. Newburgh and Marsh, quoted by Joslin (footnote 1, p. 527).

is not required, the case may be considered mild; if less than 30 units are required, moderate; and if more than 30 units, severe. This classification is sound, although the low diet would cause a negative caloric balance. The objection to it is that the diet is fixed. The degree of mildness is not determined. Another consideration is the method of administration of insulin; divided doses are far more potent than a single large dose containing the same number of units. The dextrose equivalent of insulin diminishes with increase in dosage.

It may be assumed that both methods of determining the tolerance take into account the amount of glycosuria. A criticism that may be offered is that they do not take into consideration the marked differences in renal threshold in diabetic patients. If, for example, two persons with diabetes who have different renal thresholds, but whose pancreases are equivalent so far as functional activity is concerned are put on the same diet, and this diet is in excess of their tolerance, the one with the lower renal threshold will excrete far more dextrose and will be considered to have the more severe diabetes. Although the functional activity of the pancreas is the same in each, the one with the higher threshold appears to have the milder case, because he is given more time in which to metabolize the food. The high renal threshold acts as a compensating mechanism. This phase of the subject will be amplified later.

THE DEXTROSE-TOLERANCE TEST AS A METHOD FOR THE DETERMINATION OF THE SEVERITY OF DIABETES MELLITUS

A dextrose-tolerance test was made on seventeen patients suffering from diabetes of varying degrees of severity. Each patient after fasting fourteen hours received 100 Gm. of dextrose. From each of these patients four blood specimens were taken: one, at the "fasting level," immediately before ingestion, and three at forty-five minutes, two hours, and three hours after ingestion, respectively. The sugar content of the blood was determined by the Kramer-Gittelman method [8]; blood for this test is obtained by pricking the finger tip. It was shown by Foster [9] that the content of sugar in such blood is identical with that in blood derived from the radial artery; in other words, blood from the finger tip may be considered arterial blood. In the state of fasting, the blood sugar concentration of venous is equal to that of arterial blood; after the ingestion of dextrose, however, the sugar concentration of venous becomes less than that of arterial

8. Kramer, B., and Gittelman, I. F.: Technic for Quantitative Estimation of Glucose in Small Amounts of Blood, J. A. M. A. **81**:1171 (Oct. 6) 1923.

9. Foster, G. L.: Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood, J. Biol. Chem. **55**:291 (Feb.) 1923.

blood, supposedly because the muscle cells take up dextrose. Most investigators have found the difference to be less in diabetic patients. This fact is not of importance so far as this work is concerned.

The curves portraying dextrose tolerance are recorded in table 4. The various features of the test will be discussed separately.

Dosage.—The ideal method of administration would be the timed intravenous injections as proposed by Sansum and Woodyatt.[10] They showed that in man the injection of as much as 0.85 Gm. of dextrose per kilogram of body weight per hour did not cause glycosuria. For obvious reasons, their method is not feasible for ordinary purposes. The dosage chosen in this experiment was 100 Gm. of dextrose given in the form of a 50 per cent solution. This is the amount also employed by

TABLE 4.—*Sugar Concentration of Blood and Excretion of Dextrose in Diabetes in Tests Made Periodically Following Administration of 100 Gm. of Dextrose*

	Blood Sugar Concentrations				
Case	Fasting Level, Before Ingestion	45 Minutes After Ingestion	2 Hours After Ingestion	3 Hours After Ingestion	Dextrose Excreted*
1	172	206	333	337	9.6
2	173	360	336	297	4.0
3	177	333	337	353	10.3
4	181	266	274	199	8.0
5	184	261	279	248	18.0
6	186	314	249	186	13.6
7	207	331	317	338	13.4
8	209	309	265	217	2.6
9	218	357	404	293	12.5
10	222	355	383	333	7.5
11	222	386	462	320	23.5
12	243	360	463	389	31.6
13	249	392	423	375	17.5
14	289	444	522	467	
15	298	356	428	395	16.2
16	305	444	410	370	
17	395	574	670	434	31.5

* Grams excreted in three hour period.

Hamman and Hirschman,[11] John [12] and others. Janney and Isaacson [13] gave 1.75 Gm. of dextrose per kilogram of body weight, holding that the "dextrose load" should be proportional to the weight of the individual. Gray [14] has shown that in a normal person, the maximal rise

10. Sansum, W. D., and Woodyatt, R. T.: Studies on Theory of Diabetes: VIII. Timed Intravenous Injections of Glucose at Lower Rates, J. Biol. Chem. **30**:155 (May) 1917.

11. Hamman, L., and Hirschman, I. I.: Studies in Blood Sugar, Arch. Int. Med. **20**:761 (Nov.) 1917.

12. John, H. J.: Glucose Tolerance Test and Its Value in Diagnosis, J. Metab. Research **1**:497, 1922.

13. Janney, N. W., and Isaacson, V. I.: Blood Sugar Tolerance Test, J. A. M. A. **70**:1131 (April 20) 1918.

14. Gray, H.: Blood Sugar Standards, Normal and Diabetic, Arch. Int. Med. **31**:241 (Feb.) 1923.

in blood sugar concentration is the same for a dextrose load of 20 Gm. as for one of 200 Gm. An increase in the dextrose dose administered to a diabetic person would result merely in the prolongation of the curve.

In a normal person, given 100 Gm. of dextrose on a fasting stomach, the concentration of sugar in the blood proceeds as follows: The maximal increase usually occurs at the end of one-half hour and is rarely more than from 30 to 50 per cent above the concentration at fasting level; at the end of two hours, the fasting level—and many times a value even lower than that—should be regained. Glycosuria should not occur. In diabetic patients, the curve is entirely different.

Fasting Level.—The average concentration of sugar in the blood of normal persons when fasting is 0.09 per cent. As a rule, it is higher in diabetic patients. Treatment may cause it to fall to normal. During the so-called inanition treatment, it may fall to a value below normal. The very high values are obtained in cases complicated by severe acidosis, especially those comatose and in which nephritis is present. Even in cases in which the fasting level is normal, the blood sugar concentration may rise to enormous values during a dextrose-tolerance test. As a rule, however, this is not the case. On inspection of table 4, it can be seen that, with some exceptions, the fasting level is proportional to the height of the curve. When one compares the fasting level with the amount of dextrose excreted in three hours, it is noticed that a definite relationship cannot be established between them.

Character of Curve.—In the majority of cases of diabetes, the maximal increase in dextrose concentration occurs either one hour or two hours after ingestion. This is not due to deficiency in absorption, for it is reasonable to assume that the rate of absorption in diabetic persons does not differ from that in normal persons, and in the latter the maximal blood sugar concentration usually occurs at the end of one-half hour. The blood sugar concentration does not reach the fasting level for from four to nine hours.

Glycosuria.—Hamman and Hirschman [11] and others find the renal threshold of normal persons to be about 170 mg. of dextrose per hundred cubic centimeters of blood. Roe and Irish,[15] in a study of 100 cases of diabetes, found threshold values ranging from 80 to 310. They believe that the co-existence of nephritis is the cause of the high threshold values. They also found that the threshold varies markedly in the same individual. John [12] concludes that the renal threshold for dextrose is definitely raised in many cases of diabetes, and that the more pro-

15. Roe, J. H., and Irish, D. J.: Sugar Threshold in One Hundred Diabetic Cases, J. A. M. A. **84**:1406 (May 9) 1925.

tracted and severe the case, the higher the threshold. Williams and Humphreys [16] concur in this view. Macleod [17] states that the toxic effect of a high content of sugar in the blood renders the kidney impermeable to it. Faber and Norgaard,[18] also Hagedorn,[19] occupy a unique position on this question. They do not find any relationship between the dextrose threshold and age, sex or the duration of the illness. They believe that the threshold is peculiar to each person and is immutable.

In a normal individual, the respiratory quotient during a dextrose tolerance test rises to 1, and even above 1 if there is conversion of dextrose to fat. The body suddenly flooded with dextrose concentrates on storing and oxidizing it; the metabolism of fat and protein is reduced to a minimum. It is reasonable to assume that a similar state exists in diabetic patients; that the insulin secreted by the pancreas will devote itself almost entirely to taking care of the dextrose. The obstacle which confronted one in the previous classifications, namely, that the patients were on mixed diets, has been obviated in these experiments.

I shall now consider the relationship between the amount of glycosuria and the character of the blood-sugar curve (table 4). The curve of the blood sugar concentration of case 8 is definitely higher than that of case 6, but in the latter five times as much dextrose was excreted during the three hour period. The curves for cases 13 and 15 are only slightly lower than that for case 12, but in the latter there was excretion of twice as much dextrose. The curve for case 17 is markedly higher than that for case 12, but the amount of glycosuria was the same. It can be seen that the high renal threshold causes a reduction in glycosuria. The amount of glycosuria cannot be taken as an index of the severity of diabetes.

The question now to be considered is this: To what extent may the character of the blood sugar curve—that is, the height and the length—be taken as an index of the severity of diabetes? Four possible influences on the curve must be considered: dosage, variations in absorption of dextrose, blood volume, and renal threshold.

The dose here is uniform; 100 Gm. of dextrose are given to each patient. It was stated before that Janney and Isaacson give 1.75 Gm.

16. Williams, J. R., and Humphreys, E. M.: The Clinical Significance of Blood Sugar in Diabetes Mellitus, Arch. Int. Med. **23**:546 (May) 1919.

17. Macleod, J. J. R.: Recent Work on the Physiologic Pathology of Diabetes, J. A. M. A. **62**:1222 (April 18) 1914.

18. Faber, K., and Norgaard, K.: The Relation Between Glycosuria and Glycemia, Acta med. Scandinav. **53**:666 (Jan.) 1921.

19. Hagedorn, H. C.: On the Threshold Value of Glycosuria, Acta med. Scandinav. **53**:672 (Jan.) 1921.

per kilogram of body weight. It must be remembered that in persons who are overweight there is much inactive tissue.

The volume of blood increases with increase in weight, but not directly; a thin person has proportionately more blood than an obese one. When the blood sugar concentration is high, 0.4 per cent, for instance, the total dextrose content of the blood of an obese individual may be considerably greater than that of a thin one.

It has been shown that the rate of absorption of dextrose varies considerably in different individuals.

The matter of variation in renal threshold has been discussed fully in foregoing paragraphs.

To what extent is the character of the blood sugar curve influenced by these variables? Cursorily, one would state that these factors influence it markedly. Gray [14] and many others have tested the influence of various "dextrose loads" on the character of the blood sugar curve. Gray has summarized the work of many authors. He showed that in normal persons, although the dextrose load varied from 20 to 200 Gm., the height of the blood sugar curve was the same in each case. He found that the height of the blood sugar curves in diabetic patients with the same fasting levels was the same regardless of whether the dextrose load was 50 or 100 Gm. Small doses, down to even 10 Gm., were suggested by Hamman and Hirschman, who wrote: "The general features of the diabetic sugar curve are faithfully reproduced by patients receiving, on account of the severity of the disease, smaller amounts of glucose." Apparently, the effect of the large doses is to prolong the curve. These observations, it appears to me, definitely reduce the variables mentioned to negligible factors.

A most important function of the pancreas (insulin) is to maintain a normal blood sugar concentration. The functional activity of the pancreas may be judged by its ability to do so. The height of the blood sugar curve may tentatively be accepted as an index of the severity of the diabetes. The severity is not directly proportional to the height of the curve, for it has been shown by Allan [20] and others that the dextrose equivalent of insulin is greater when the dose of insulin is reduced and also when the amount of dextrose is increased.

The patients were on maintenance diets previous to the performance of the dextrose tolerance test. The test is not valid when made on diabetic patients who have fasted several days, for it has been shown that normal rabbits who have been kept from food for several days will have diabetic dextrose tolerance curves.

A question which is relevant to this subject is this: Does the administration of dextrose lead to a breaking down of tolerance? Carbo-

20. Allan, F. N.: Glucose Equivalent of Insulin in Depancreated Dogs, Am. J. Physiol. **67**:275 (Jan.) 1924.

hydrate has always been considered the bête noire of diabetic persons. Joslin [21] deprecates the use of dextrose-tolerance test, although he has never seen a diabetic patient injured by it. Ohler [22] also argues that on theoretical grounds the giving of large quantities of dextrose is harmful. Hamman and Hirschman,[10] in the dextrose-tolerance tests performed on diabetic persons, used from 10 to 100 Gm. of dextrose, depending on the severity of the case. Allen,[23] in his work on partially depancreatized dogs, found that excessive feeding of carbohydrates, especially when given in a readily absorptive form, such as dextrose, leads to a rapid breaking down of tolerance. He elaborates on the theory of "overstrain" of the b-cells of the islands of Langerhans, which leads to hydropic degeneration. However, there is no other animal tissue, so far as I am aware, in which structural changes similar to those observed in the islands occur as a result of overstrain. Macleod [24] states: "It would be almost unique as an etiological factor, the only other known instance being in an experiment by Barany, in which structural changes were observed to occur in the cells of the nucleus acusticus as a result of the receipt by them of persistent sound impressions." Jensen and Carlson [25] agree with Macleod and state that the usual result of overstrain is marked hypertrophy, not atrophy. Wilder and his associates [4] showed that the dextrose derived from protein requires far more insulin for metabolism than do the carbohydrates. I observed for several months seven patients who had had two dextrose tolerance tests performed two days apart. None of these patients showed the slightest change in tolerance as a result of this procedure. I believe that it is innocuous.

SUMMARY AND CONCLUSIONS

Various methods for determining the severity of diabetes are discussed. Classifications which take into account only the amount of glycosuria are fallacious, for insulin is concerned with the metabolism of all foods—carbohydrates, proteins and fats. Such classifications are also vitiated by the fact that the renal threshold for dextrose is

21. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 170.

22. Ohler, W. R.: Lessons to Be Learned from Repeated Glucose Tolerance Tests, Med. Clin. N. Amer. **5**:1465 (March) 1922.

23. Allen, F. M.: Production and Control of Diabetes in the Dog, Effects of Carbohydrate Diets, J. Exper. Med. **31**:381 (April) 1920.

24. Macleod, J. J. R.: Carbohydrate Metabolism and Insulin, New York, Longmans, Green and Company, 1926, p. 53.

25. Jensen, W. W., and Carlson, A. J.: Apparent Influence of Diet of Carbohydrates on Pancreas Remnant of Partially Pancreatectomized Dogs, Am. J. Physiol. **51**:423, 1920.

different for each person. A high renal threshold, which acts as a compensating mechanism, would mask a severe case.

The dextrose tolerance test as a method for determining the severity of diabetes is considered. It is shown that the amount of glycosuria occurring during the test cannot be taken as an index of severity because of differences in renal threshold in different individuals. It is shown that the height of blood sugar curve in such tests, however, may be accepted as a criterion of the gravity of diabetes.

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Book Reviews

PATHOLOGICAL PHYSIOLOGY OF INTERNAL DISEASES. FUNCTIONAL PATHOLOGY. By ALBION WALTER HEWLETT. Revised in memoriam by his colleagues. With 164 illustrations. New York: D. Appleton & Company, 1928.

The third edition has been prepared from the notes left by Doctor Hewlett and represents a memorial tribute to the great clinician and physiologist who died in the prime of life. There has been a complete and thorough revision of the entire volume so as to include recent developments in physiologic and clinical fields.

To the chapter on the heart are added the theory of circus movement, the use of quinidine in auricular fibrillation, the discussion of clinical ventricular fibrillation, and mention of the new work on the relation of the cervical sympathetic to angina pectoris.

The chapter on digestion includes the recent work of Ivy on the various phases of gastric secretion, Bloomfield and Keefer's method of gastric analysis and other aspects of gastro-intestinal physiology. Insulin is included in the discussion of diabetes mellitus, and the newer work on the relationship of changes in the energy metabolism to obesity is taken up. The discussion of the vitamins has been brought up to date down to vitamin E.

The chapter on the acid base equilibrium has been extensively modified and enlarged to make room for the work of the Henderson and Van Slyke schools, and is really a model chapter. The same comment applies to the chapters on respiration and carbohydrate metabolism. In the discussion of renal function, perhaps too much space is given to Schlayer's tests and insufficient mention made of the urea concentration tests as devised by Addis and others. Furthermore, renal edema is still discussed largely from Widal's point of view and not enough from the physiologic aspects of fluid exchange, including the question of the osmotic pressure of plasma proteins and other factors. It seems to the reviewer that the plasma proteins might be taken up in a chapter on renal edema rather than in a discussion of "hydremia," because the latter term itself might just as well be left out entirely in view of its misinterpretation by many.

Taken as a whole, however, this book represents probably the best of its kind not only in the English language but in any language, and is, therefore, a fitting tribute to the memory of the late Doctor Hewlett.

SYPHILIS UND INNERE MEDIZIN, III. DIE SYPHILIS DES ZIRCULATIONS- UND RESPIRATION-TRAKTES UND DER INNERSEKRETORISCHEN DRÜSEN. SYPHILIS UND BLUTKRANKHEITEN. By H. SCHLESINGER, Director of the third medical division, Allgemeine Krankenhaus, Vienna. Pp. 234. Price, 18 marks. Vienna: Julius Springer, 1928.

This volume comprises a fairly complete treatment of the many aspects of syphilis of the cardiovascular system, endocrine glands and the relation between syphilis and diseases of the blood. Syphilis of the pulmonary system and the special problems presented by coincidental syphilis and pulmonary tuberculosis are considered fully.

The more important subjects are taken up according to pathology, diagnosis, prognosis and therapy. The more uncommon conditions are aptly illustrated by the author's own cases. General syphilologic principles are interwoven more adequately than in most publications from the internist's pen.

A few American authors are quoted. The author states that antisyphilitic therapy is becoming more and more the function of the general practitioner, internist and neurologist. This is in contrast to the situation in this country, where antisyphilitic therapy has reached a higher degree of perfection, encouraging

centralization under one head, with excellent diagnostic and follow-up cooperation on the part of other specialists.

The author erroneously states that original "salvarsan" is the drug of choice for therapy of cardiovascular syphilis in this country, and does not mention the extensive use, intramuscularly, of sulpharsphenamine for the purpose of avoiding vascular shock in these cases. He discusses the arsenical spirocide (acetarsone [stovarsol]) for oral administration.

It is advantageous to restrict the activities of patients with syphilitic aortitis more rigorously than suggested. It would hardly be advisable to allow an American patient to partake of dancing, swimming and physical sports, even in restricted measure.

This work fills a real need for a more or less encyclopedic treatment of these internal medical problems in the realm of syphilology.

LOCAL IMMUNIZATION. By A. BESREDKA, translated by HARRY PLOTZ. Price, $3.50. Baltimore: Williams and Wilkins Company, 1927.

This small book is divided in five chapters, Anthrax, Staphylococcus, Streptococcus Infections, Dysentery, and Typhoid Fevers; the last chapter is devoted to a discussion of theory.

The chapter on anthrax is the best of the group. The experimental evidence is most convincing. The staphylococcus is next in order of completeness. The chapters on dysentery and on typhoid are not so thoroughly treated. "Bilivaccin" pills that are used so extensively in oral vaccination are not described any place in the book. The wet dressings with filtered staphylococcus cultures or the "antivirus" (Besredka) should be of general interest as a prophylactic active immunization procedure. There are great possibilities for the use of streptococcus in this connection.

The book is well written and is easy to read. The whole theory is something new and opens up a large and almost unexplored field.

DENTAL INFECTION AND SYSTEMIC DISEASE. By RUSSELL L. HADEN. Price $2.50. Illustrated with 63 engravings. Philadelphia: Lea & Febiger, 1928.

In this small, well illustrated volume, there is an excellent presentation of the problems of dental infection and a good description of the radiographic and clinical methods of diagnosis. Unfortunately, the author's views and his experimental work are so saturated with an uncritical enthusiasm for Rosenow's theory of "elective localization" that the book is full of misrepresentations and dogmatic statements. The attempt to diagnose metastatic infection in patients from the results of inoculation into animals of bacteria obtained from roots of teeth is almost ludicrous as it is presented in some of the case reports. One wonders why rabbits do not develop "elective localization" of bacteria in the site most frequently involved in patients—the peri-apical tissues of the teeth. The author comes back to earth and to solid clinical common sense in parts of the concluding chapter when he discusses what should be done for focal dental infection in various types of patients.

PRACTICAL GASTROSCOPY. By JEAN RACHET, M.D., Paris. Authorized Translation by FRED. F. IMIANITOFF, Brussels. Price, $5.50. Pp. 148. New York: William Wood & Company, 1927.

This book is a complete survey of the subject of gastroscopy. After a brief prelude of the historical periods and the principles underlying the design of a gastroscope, the author proceeds to the gastroscopic examination, bringing out clearly its indications and contraindications. In chapter IV he presents the results obtained and shows several excellent roentgenograms. His conclusions as to the results obtained, and the future of gastroscopy are those of one well acquainted with his subject. The book can be recommended to all interested in this phase of gastro-intestinal work.